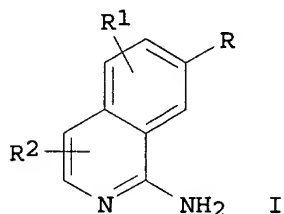


AN 1999:184268 CAPLUS
 DN 130:223587
 TI 1-amino-7-isoquinoline derivatives as serine protease inhibitors
 IN Liebeschuetz, John Walter; Wylie, William Alexander; Waszkowycz, Bohdan; Murray, Christopher William; Rimmer, Andrew David; Welsh, Pauline Mary; Jones, Stuart Donald; Roscoe, Jonathan Michael Ernest; Young, Stephen Clinton; Morgan, Phillip John; Camp, Nicholas Paul; Crew, Andrew Philip Austin
 PA Proteus Molecular Design Ltd., UK
 SO PCT Int. Appl., 89 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9911657	A1	19990311	WO 1998-GB2600	19980828 <--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9888753	A1	19990322	AU 1998-88753	19980828
	EP 1012166	A1	20000628	EP 1998-940425	19980828
	R: CH, DE, ES, FR, GB, IT, LI, NL				
	US 6262069	B1	20010717	US 2000-485677	20000225
	US 2002040144	A1	20020404	US 2001-865418	20010529
	US 6420438	B1	20020716	US 2000-865418	20010529
PRAI	GB 1997-18392	A	19970829		
	GB 1998-3173	A	19980213		
	WO 1998-GB2600	W	19980828		
	US 2000-485677	A1	20000225		
OS	MARPAT 130:223587				
GI					



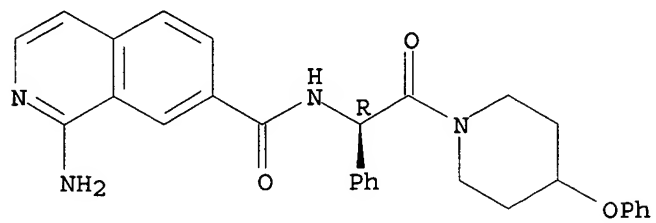
AB Aminoisoquinoline amino acid derivs. I [R1 = H, halo, cyano, nitro, hydroxy, amino, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, thiol, alkylthio, aminosulfonyl, alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or alkylamino (optionally substituted); R2 = H, halo, Me, amino, hydroxy, or oxo; and R is X-X-Y(R7)-L-Lp(D)n, where each X independently is a C, N, O or S atom or a CO, CR1, CR12 or NR1 group; Y is a nitrogen atom or a CR1 group or Y and L taken together form a cyclic group; R7 is a lipophilic group selected from alkyl, alkenyl, mono- or bi-cycloalkyl, aryl, heteroaryl, mono- or bicycloalkylalkyl, mono- or bicycloalkylalkenyl, aralkyl, heteroaryl-alkyl, arylalkenyl, heteroarylalkenyl, all optionally substituted by a group R1; L is an org. linker group contg. 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic

group; Lp is a lipophilic org. group selected from alkyl, heterocyclic, alkenyl, alkaryl, cycloalkyl, polycycloalkyl, cycloalkenyl, aryl, aralkyl or haloalkyl group or a combination of two or more such groups optionally substituted by one or more of oxa, thia, aza or R1 groups; D is a hydrogen bond donor group; and n is 0, 1, or 2] or their 3,4-dihydro derivs. were prepd. as serine protease inhibitors. Thus, 1-aminoisoquinolin-7-oyl-D-phenylglycine-4-methoxybenzylamide was prepd. by amidation of Boc-D-phenylglycine with 4-methylbenzylamine, followed by deprotection and coupling with 1-aminoisoquinoline-7-carboxylic acid trifluoroacetate.

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IN 7-Isoquinolinecarboxamide, 1-amino-N-[(1R)-2-oxo-2-(4-phenoxy-1-piperidinyl)-1-phenylethyl] - (9CI)
MF C29 H28 N4 O3

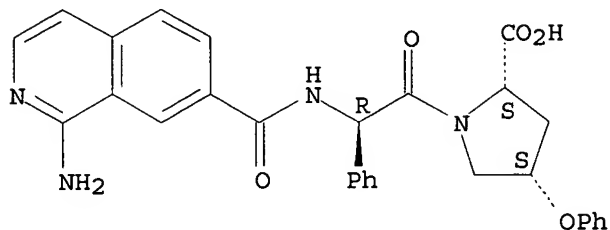
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

IN L-Proline, (2R)-N-[(1-amino-7-isoquinolinyl)carbonyl]-2-phenylglycyl-4-
phenoxy-, (4S)- (9CI)
MF C29 H26 N4 O5

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 15

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=> s 16 ful
FULL SEARCH INITIATED 14:52:33 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 49599 TO ITERATE
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6 ANSWERS

L8 6 SEA SSS FUL L6

=> s 18

L9 5 L8

=> d bib abs hitstr 1-5

L9 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS

AN 2002:964146 CAPLUS

DN 138:39187

TI Preparation of piperidinecarboxylates and related compounds as NMDA NR2B receptor antagonists for the treatment or prevention of migraine.

IN Allen, Christopher; Koblan, Ken S.; Sleeth, Timothy

PA Merck & Co., Inc., USA

SO PCT Int. Appl., 185 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002100352	A2	20021219	WO 2002-US21069	20020607
	WO 2002100352	A3	20030327		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-297672P P 20010612

AB A method for treating or preventing migraines comprises administration of an NR2B receptor antagonist (no data). The invention also encompasses the combination of an NR2B antagonist with a cyclooxygenase-2 selective inhibitor, a calcitonin gene-related peptide receptor (CGRP) ligand, a leukotriene receptor antagonist, or a 5HT1B/1D agonist for the treatment or prevention of migraines. Thus, 4-hydroxybenzoic acid, 1-hydroxybenzotriazole hydrate, benzyl 4-(aminomethyl)piperidine-1-carboxylate (prepn. given), and Et3N in DMF were treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and the mixt. allowed to stir at room temp. for 18 h to give 4-[(4-hydroxybenzoylamino)methyl]piperidine-1-carboxylic acid benzyl ester.

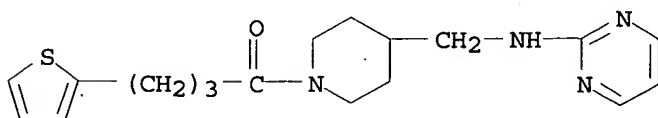
IT 455266-25-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of piperidinecarboxylates and related compds. as NR2B receptor antagonists for the treatment or prevention of migraine)

RN 455266-25-8 CAPLUS

CN 4-Piperidinemethanamine, 1-[1-oxo-4-(2-thienyl)butyl]-N-2-pyrimidinyl-(9CI) (CA INDEX NAME)

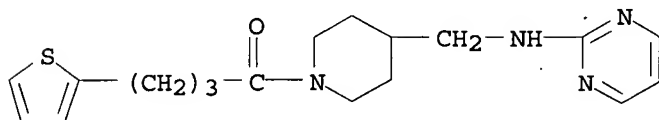


L9 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS

AN 2002:676010 CAPLUS

DN 137:216875
 TI Preparation of N-acyl-4-(heterocyclylaminomethyl)piperidines as NMDA/NR2B antagonists
 IN Claiborne, Christopher F.; Butcher, John W.; Claremon, David A.; Libby, Brian E.; Liverton, Nigel J.; Munson, Peter M.; Nguyen, Kevin T.; Phillips, Brian; Thompson, Wayne; McCauley, John A.
 PA Merck & Co., Inc., USA
 SO PCT Int. Appl., 208 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002068409	A1	20020906	WO 2002-US5226	20020220
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002165241	A1	20021107	US 2002-79452	20020220
PRAI	US 2001-271100P	P	20010223		
OS	MARPAT 137:216875				
AB	BQ1(X)ANHQ2 [Q1 = 5-7 membered N-contg. nonarom. ring, azabicyclooctyl; Q2 = 5-6 membered (substituted) heteroaryl ring; A = alkylene; B = Ar(CH2)0-3O2C, Ar(CH2)0-3SO2, etc.; Ar = (substituted) aryl, heteroaryl; X = H, OH, F, alkyl, alkoxy, NH2, O], were prepd. Thus, 1-[(benzyloxy)carbonyl]-4-piperidinecarboxylic acid, 4-aminopyridine, EDC, and HOAt were kept 4 h in DMF to give the amide, which was reduced with BH3.THF to give benzyl 4-[(4-pyridylamino)methyl]-1-piperidinecarboxylate. Title compds. showed IC50's of <50 .mu.M for inhibition of NR1A/2B NMDA receptor activation.				
IT	455266-25-8P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (claimed compd.; prepn. of N-acyl-4-(heterocyclylaminomethyl)piperidine s as NMDA/NR2B antagonists)				
RN	455266-25-8 CAPLUS				
CN	4-Piperidinemethanamine, 1-[1-oxo-4-(2-thienyl)butyl]-N-2-pyrimidinyl-(9CI) (CA INDEX NAME)				



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
 AN 2002:484686 CAPLUS
 DN 137:47124
 TI Preparation of 2-[(carbamoylmethyl)carbamoyl]phenylpropanoates and analogs as .alpha.v.beta.3 integrin receptor ligands
 IN Geneste, Herve; Kling, Andreas; Lange, Udo; Lauterbach, Arnulf; Seitz, Werner; Graef, Claudia Isabella; Subkowski, Thomas; Hornberger, Wilfried;

Kluge, Michael; Spriesterbach, Rainer
 PA Knoll A.-G., Germany
 SO Ger. Offen., 62 pp.
 CODEN: GWXXBX
 DT Patent
 LA German
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 10064823	A1	20020627	DE 2000-10064823	20001222
	WO 2002051810	A2	20020704	WO 2001-EP14924	20011218
	WO 2002051810	A3	20030320		

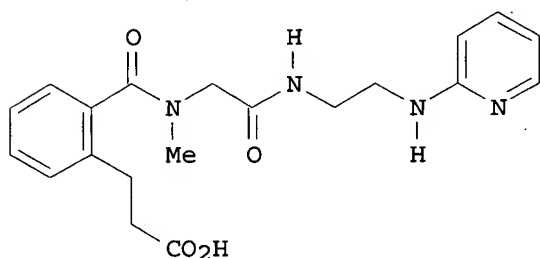
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI DE 2000-10064823 A 20001222

OS MARPAT 137:47124

GI



I

AB Title compds. were prepd. as .alpha.v.beta.3 integrin receptor ligands (no data). Thus, 2-(OHC)C6H4CO2H was condensed with (EtO)2P(O)CH2CO2Me and the hydrogenated product amidated by MeNHCH2CO2CMe3 to give, after sapon., 2-(HO2CH2CH2C)C6H4CONMeCH2CO2H which was amidated by N-(2-pyridinyl)ethandiamine to give, after sapon., title compd. I.

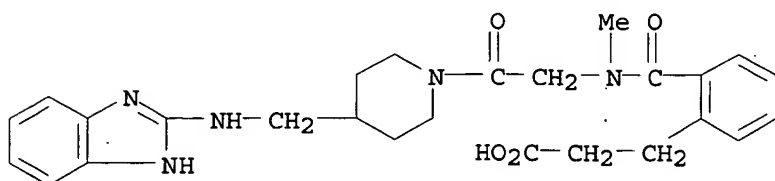
IT 438633-38-6P 438633-41-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

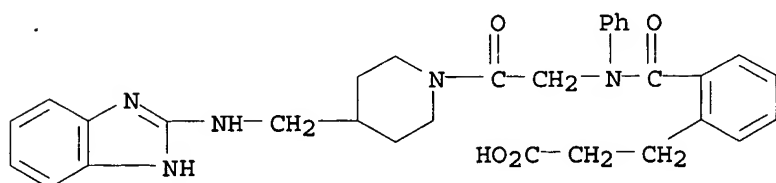
(prepn. of 2-[(carbamoylmethyl)carbamoyl]phenylpropanoates and analogs as .alpha.v.beta.3 integrin receptor ligands)

RN 438633-38-6 CAPLUS

CN Benzenepropanoic acid, 2-[[[2-[4-[(1H-benzimidazol-2-ylamino)methyl]-1-piperidinyl]-2-oxoethyl]methylamino]carbonyl]- (9CI) (CA INDEX NAME)



RN 438633-41-1 CAPLUS
 CN Benzenepropanoic acid, 2-[[[2-[4-[(1H-benzimidazol-2-ylamino)methyl]-1-piperidiny]]-2-oxoethyl]phenylamino]carbonyl]- (9CI) (CA INDEX NAME)



L9 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
 AN 2001:923766 CAPLUS
 DN 136:54019
 TI Preparation of amino acid derivatives as serine protease inhibitors
 IN Liebeschuetz, John Walter; Murray, Christopher William; Young, Stephen Clinton; Camp, Nicholas Paul; Jones, Stuart Donald; Wylie, William Alexander; Masters, John Joseph; Wiley, Michael Robert; Sheehan, Scott Martin; Engel, David Birenbaum; Watson, Brian Morgan
 PA Eli Lilly and Company, USA
 SO PCT Int. Appl., 120 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 13

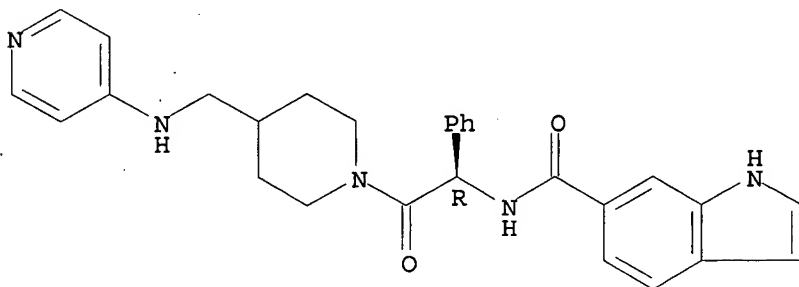
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001096304	A1	20011220	WO 2001-GB2572	20010612
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	WO 2000076971	A2	20001221	WO 2000-GB2302	20000613
	WO 2000076971	A3	20010802		
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1289953	A1	20030312	EP 2001-938403	20010612
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2002151724	A1	20021017	US 2002-30186	20020204
PRAI	WO 2000-GB2302	W	20000613		
	GB 2000-30306	A	20001213		
	GB 1999-13823	A	19990614		
	US 1999-142064P	P	19990702		
	GB 1999-18741	A	19990809		
	GB 1999-29553	A	19991214		
	WO 2001-GB2572	W	20010612		

OS MARPAT 136:54019
 AB Compds. R2-X-X-Y(Cy)-L-Lp(D)n [R2 is a 5- or 6-membered arom. carbon ring optionally interrupted by a N, O or S ring atom, optionally substituted at the 3 and/or 4 position or forms a fused ring system at these positions, which is an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring, or substituted at the position alpha to X-X; X is a C, N, O or S atom or a CO, CR1a, C(R1a)2 or NR1a group, where R1a represents H, OH, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy carbonyl, alkylaminocarbonyl, alkoxy carbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by OH, alkylamino, alkoxy, oxo, aryl or cycloalkyl; Y is a N atom or a CR1b group (R1b defined as for R1a); Cy is an (un)substituted, (un)satd., mono- or polycyclic, homo- or heterocyclic group; -L-Lp(D)n is 3-(Rq-CH2)-1-pyrrolidinylcarbonyl or 4-(Rq-CH2)-1-piperidinylcarbonyl, where Rq is an amino group] or their physiol.-tolerable salts were prepd. for use as serine protease and factor Xa inhibitors in the treatment of cardiovascular disorders. Compds. of the invention were found to significantly elongate the partial thromboplastin time (prothrombin time). Thus, 1-[(4-methoxybenzoyl-D-phenylglyciny)]-4-[(isopropylamino)methyl]piperidine hydrochloride was prepd. in the first of 28 examples.

IT 381216-02-0P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of amino acid derivs. as serine protease inhibitors)

RN 381216-02-0 CAPLUS
 CN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-[(4-pyridinylamino)methyl]-1-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS
 AN 2001:661421 CAPLUS
 DN 135:226988
 TI Preparation of condensed thiazolamines as neuropeptide Y5 antagonists
 IN Schmidlin, Tibur; Rueeger, Heinrich; Gerspacher, Marc
 PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft M.B.H.
 SO PCT Int. Appl., 41 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001064675	A1	20010907	WO 2001-EP2339	20010301
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

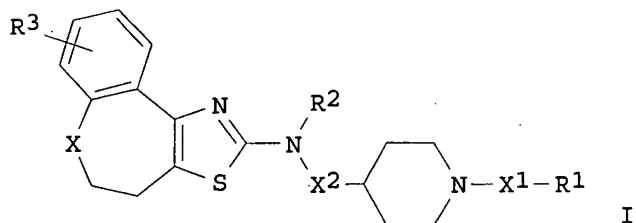
CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
 HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
 LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
 RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
 VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI DE 2000-10010475 A 20000303

DE 2000-10010476 A 20000303

OS MARPAT 135:226988

GI



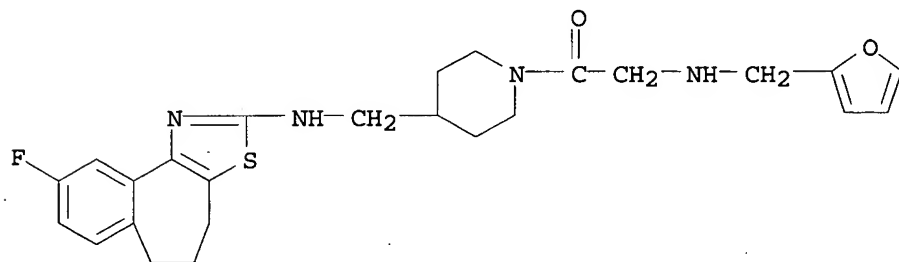
AB The title compds. [I; R1 = (un)substituted alkyl, cycloalkyl, Ph, etc.; R2 = H, SO3H, PO3H2; R3 = H, alkyl, alkoxy, etc.; X = CH2, O; X1 = CO, SO2; X2 = alkylene] and their pharmaceutically acceptable salts which act against the binding of the neuropeptide Y (NPY) to the Y5-receptor subtype (NPY-antagonism), and might be used in particular for the treatment of adiposity, were prepd. and formulated. E.g., a multi-step synthesis of I [R1 = Me; R2 = H; R3 = 9-F; X = CH2; X1 = CO; X2 = CH2] which showed a redn. in food intake of 57% in rats, was given.

IT 359017-45-1P 359018-33-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of condensed thiazolamines as neuropeptide Y5 antagonists)

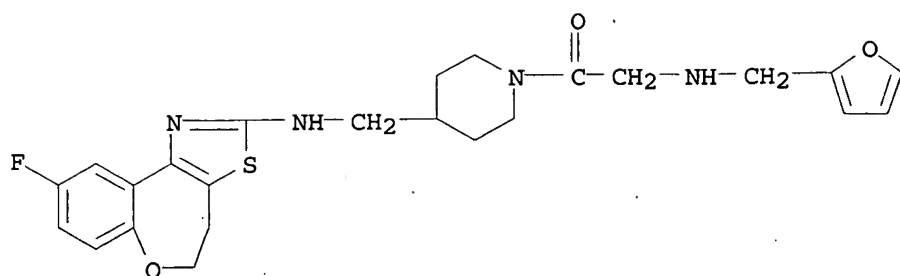
RN 359017-45-1 CAPLUS

CN 4-Piperidinemethanamine, N-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[1,2-d]thiazol-2-yl)-1-[[2-(furanylmethyl)amino]acetyl]- (9CI) (CA INDEX NAME)



RN 359018-33-0 CAPLUS

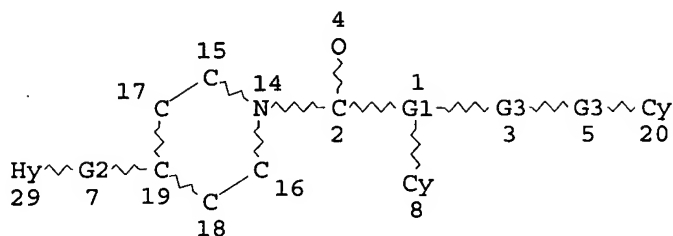
CN 4-Piperidinemethanamine, N-(9-fluoro-4,5-dihydro[1]benzoxepino[5,4-d]thiazol-2-yl)-1-[[2-(furanylmethyl)amino]acetyl]- (9CI) (CA INDEX NAME)



RE.CNT 5

THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d 17
 L7 HAS NO ANSWERS
 L7 STR



VAR G1=C/N
 VAR G2=O/N
 VAR G3=C/O/S/N
 NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RSPEC 14
 NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE

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100.0% PROCESSED 63168 ITERATIONS
 SEARCH TIME: 00.00.04

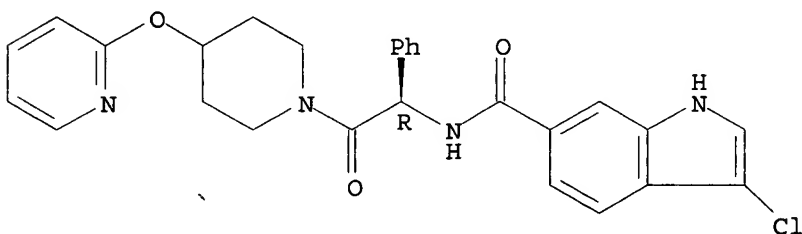
41 ANSWERS

L9 41 SEA SSS FUL L7

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L9 41 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[4-(2-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)
 MF C27 H25 Cl N4 O3
 CI COM

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

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COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

195.45

195.66

FILE 'CAPLUS' ENTERED AT 09:48:27 ON 20 JUN 2003

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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FILE COVERS 1907 - 20 Jun 2003 VOL 138 ISS 26

FILE LAST UPDATED: 19 Jun 2003 (20030619/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L10 3 L9

=> d bib 1-3

L10 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS

AN 2001:923758 CAPLUS

DN 136:37946

TI Preparation of amino acid derivatives as serine protease inhibitors

IN Liebeschuetz, John Walter; Murray, Christopher William; Young, Stephen Clinton; Camp, Nicholas Paul; Jones, Stuart Donald; Wylie, William Alexander; Masters, John Joseph; Wiley, Michael Robert; Sheehan, Scott Martin; Engel, David Birenbaum; Watson, Brian Morgan

PA Eli Lilly and Company, USA

SO PCT Int. Appl., 142 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001096296	A1	20011220	WO 2001-GB2541	20010612
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	WO 2000076971	A2	20001221	WO 2000-GB2302	20000613
	WO 2000076971	A3	20010802		

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 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1289950 A1 20030312 EP 2001-938386 20010612

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US 2003078438 A1 20030424 US 2002-30189 20020204

PRAI WO 2000-GB2302 W 20000613
 GB 2000-30303 A 20001213
 GB 1999-13823 A 19990614
 US 1999-142064P P 19990702
 GB 1999-18741 A 19990809
 GB 1999-29553 A 19991214
 WO 2001-GB2541 W 20010612

OS MARPAT 136:37946

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS

AN 2000:900614 CAPLUS

DN 134:56958

TI Preparation of amino acid derivatives as serine protease inhibitors

IN Liebeschuetz, John Walter; Lyons, Amanda Jane; Murray, Christopher
 William; Rimmer, Andrew David; Young, Stephen Clinton; Camp, Nicholas
 Paul; Jones, Stuart Donald; Morgan, Phillip John; Richards, Simon James;
 Wylie, William Alexander; Masters, John Joseph; Wiley, Michael Robert

PA Eli Lilly and Company, USA; Protherics Molecular Design Limited

SO PCT Int. Appl., 261 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 13

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	EP 1192132	A2	20020403	EP 2000-938916	20000613
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	WO 2001096296	A1	20011220	WO 2001-GB2541	20010612
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US 2002151724	A1	20021017	US 2002-30186 20020204
US 2003078438	A1	20030424	US 2002-30189 20020204
US 2003109706	A1	20030612	US 2002-30188 20020204
NO 2002005665	A	20021125	NO 2002-5665 20021125
PRAI GB 1999-13823	A	19990614	
US 1999-142064P	P	19990702	
GB 1999-18741	A	19990809	
GB 1999-29553	A	19991214	
WO 2000-GB2302	A	20000613	
GB 2000-30303	A	20001213	
GB 2000-30304	A	20001213	
GB 2000-30305	A	20001213	
GB 2000-30306	A	20001213	
WO 2001-GB2541	W	20010612	
WO 2001-GB2551	W	20010612	
WO 2001-GB2553	W	20010612	
WO 2001-GB2572	W	20010612	

L10 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

AN 2000:900613 CAPLUS

DN 134:56957

TI Preparation of amino acid derivatives as serine protease inhibitors

IN Liebeschuetz, John Walter; Lyons, Amanda Jane; Murray, Christopher William; Rimmer, Andrew David; Young, Stephen Clinton; Camp, Nicholas Paul; Jones, Stuart Donald; Morgan, Phillip John; Richards, Simon James; Wylie, William Alexander; Lively, Sarah Elizabeth; Harrison, Martin James; Waszkowycz, Bohdan; Masters, John Joseph; Wiley, Michael John

PA Eli Lilly and Company, USA; Protherics Molecular Design Limited

SO PCT Int. Appl., 350 pp.

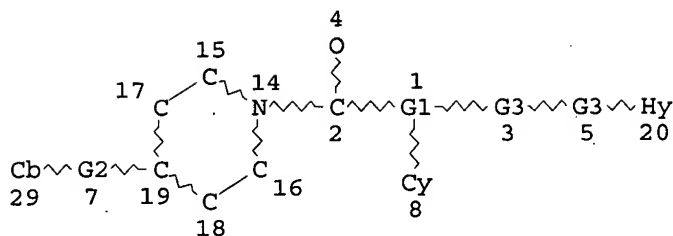
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 13

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	WO 2000076970	A3	20010719		
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	EP 1192135	A2	20020403	EP 2000-938912	20000613
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	US 1999-142064P	P	19990702		
	GB 1999-18741	A	19990809		
	GB 1999-29552	A	19991214		
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	WO 2000-GB2296	W	20000613		
OS	MARPAT 134:56957				



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 SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
 BATCH **COMPLETE**
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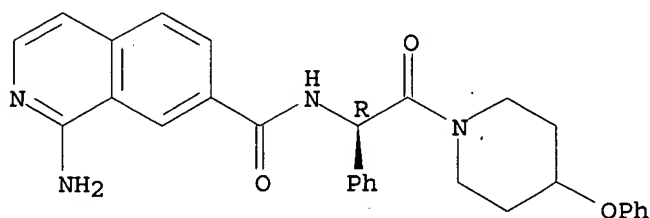
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L13 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
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 CN 7-Isoquinolinecarboxamide, 1-amino-N-[(1R)-2-oxo-2-(4-phenoxy-1-piperidinyl)-1-phenylethyl]- (9CI) (CA INDEX NAME)
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 MF C29 H28 N4 O3
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



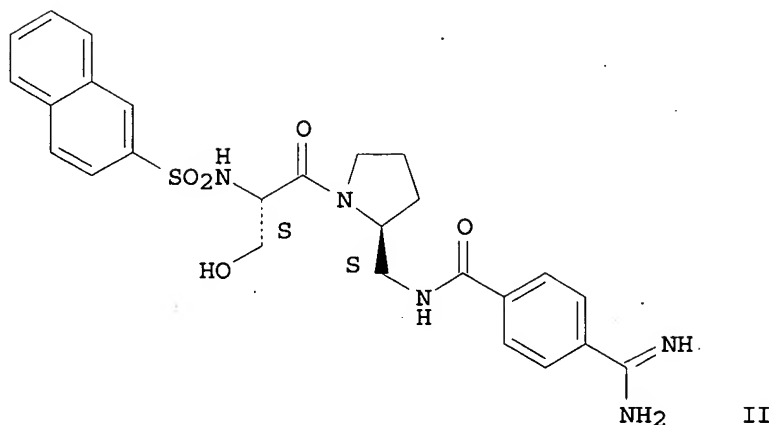
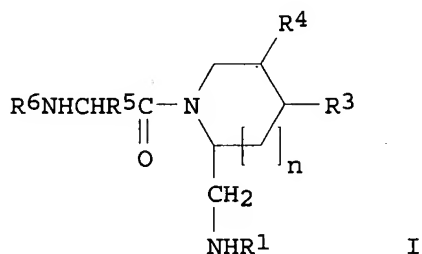
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)

1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

AN 1995:807929 CAPLUS
 DN 123:227995
 TI Preparation of guanidinyl- or amidinyl-substituted N-acylpyrrolidines and N-acylpiperidines as thrombin inhibitors.
 IN Kimball, Spencer D.; Das, Jagabandhu; Lau, Wan Fang
 PA Bristol-Myers Squibb Co., USA
 SO Eur. Pat. Appl., 81 pp.
 CODEN: EPXXDW
 DT Patent
 LA English
 FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 623596	A1	19941109	EP 1994-106853	19940502
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	JP 06340619	A2	19941213	JP 1994-88296	19940426
	CA 2122646	AA	19941104	CA 1994-2122646	19940502
	AU 9461837	A1	19941110	AU 1994-61837	19940502
	AU 669432	B2	19960606		
PRAI	US 1993-56017	A	19930503		
OS	MARPAT 123:227995				
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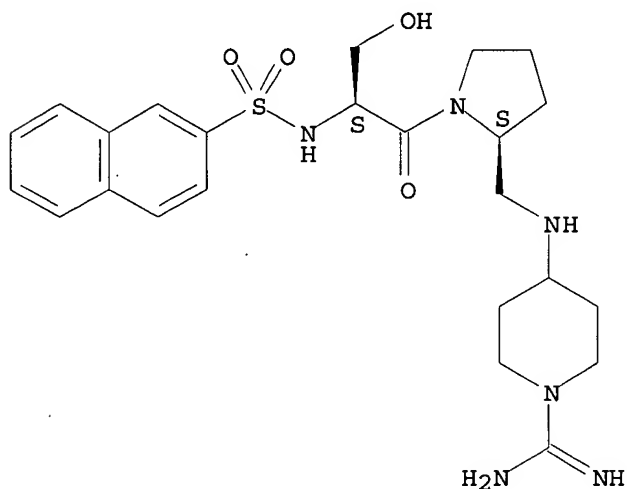
AB Guanidinyl- or amidinyl-substituted N-acylpyrrolidines and N-acylpiperidines I (n = integer; R1 = guanidine, amidine, amino-linking group; R3, R4 = H, alkyl, cycloalkyl, etc.; R5 = H, hydroxyalkyl, etc.; R6 = H, carboxy, etc.) were disclosed as thrombin inhibitors. A specifically claimed example compd. is amidino-N-[[[hydroxy[[[naphthalenyl]sulfonyl]amino]oxopropyl]pyrrolidinyl]methyl]benzamide II.
 IT 168050-92-8

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of guanidiny- or amidiny- pyrrolidines or piperidines
antithrombotics)

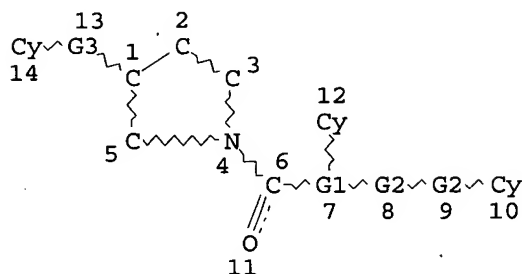
RN 168050-92-8 CAPLUS

CN 2-Pyrrolidinemethanamine, N-[1-(aminoiminomethyl)-4-piperidinyl]-1-[3-
hydroxy-2-[(2-naphthalenylsulfonyl)amino]-1-oxopropyl]-, [S-(R*,R*)]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



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 L1 HAS NO ANSWERS
 L1 STR



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 VAR G2=O/S/C/N
 VAR G3=O/N
 NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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 NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE

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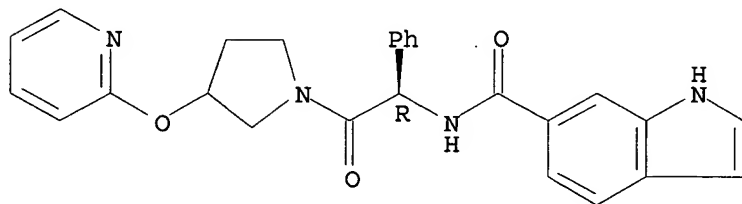
12 ANSWERS

L3 12 SEA SSS FUL L1

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L3 ANSWER 1 OF 12 REGISTRY COPYRIGHT 2003 ACS
 RN 313488-49-2 REGISTRY
 CN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(2-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C26 H24 N4 O3
 SR CA
 LC STN Files: CA, CAPLUS

Absolute stereochemistry.

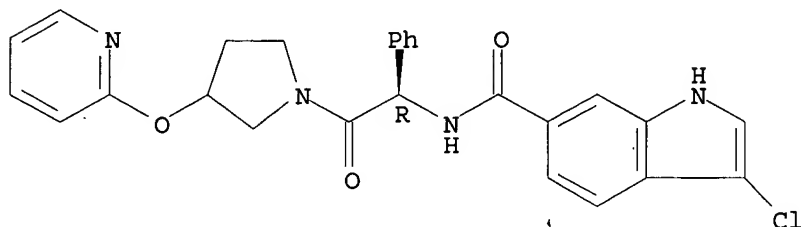


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3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 2 OF 12 REGISTRY COPYRIGHT 2003 ACS
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LC STN Files: CA, CAPLUS

Absolute stereochemistry.

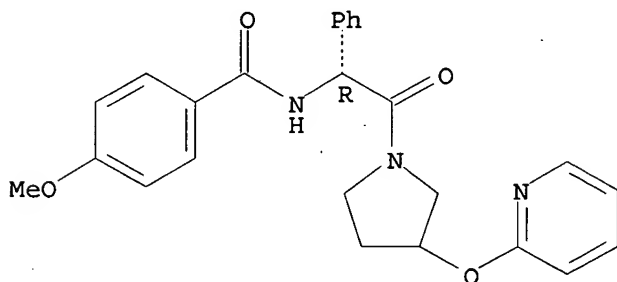


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3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

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RN 313488-47-0 REGISTRY
CN Benzamide, 4-methoxy-N-[(1R)-2-oxo-1-phenyl-2-[3-(2-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
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LC STN Files: CA, CAPLUS

Absolute stereochemistry.



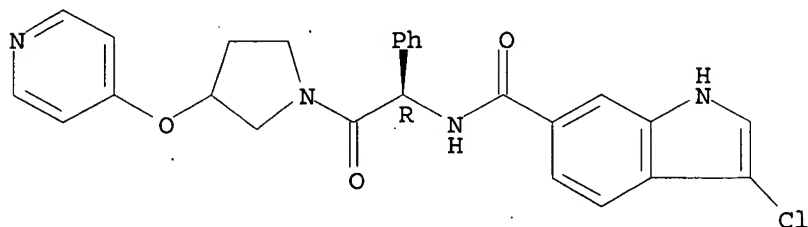
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 4 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-46-9 REGISTRY

CN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H23 Cl N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

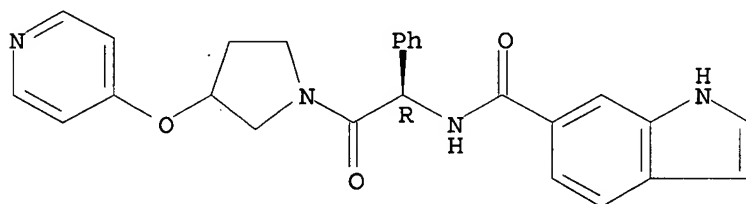


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 5 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-45-8 REGISTRY
CN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H24 N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

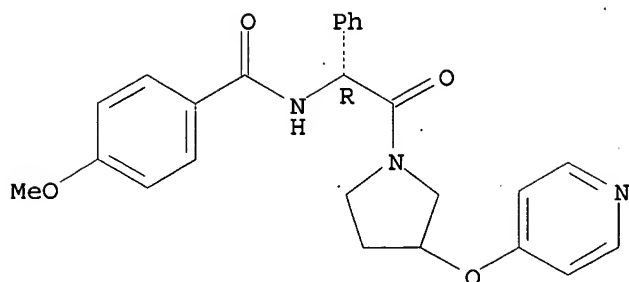


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 6 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-44-7 REGISTRY
CN Benzamide, 4-methoxy-N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H25 N3 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

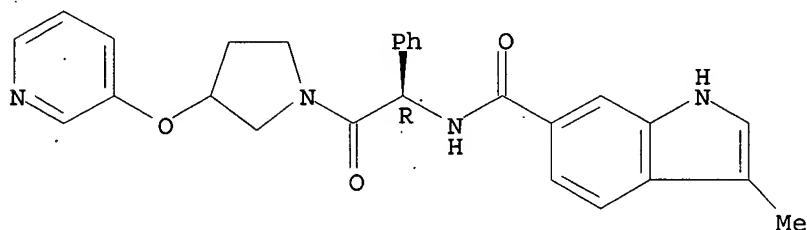


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 7 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-04-9 REGISTRY
CN 1H-Indole-6-carboxamide, 3-methyl-N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H26 N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

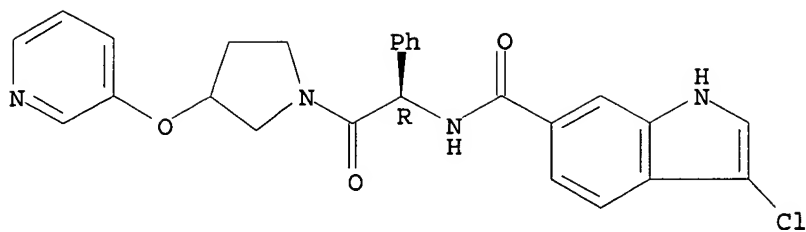


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 8 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-03-8 REGISTRY
CN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H23 Cl N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

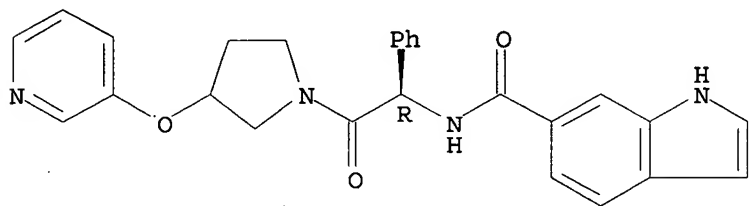


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 9 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313488-02-7 REGISTRY
CN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H24 N4 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

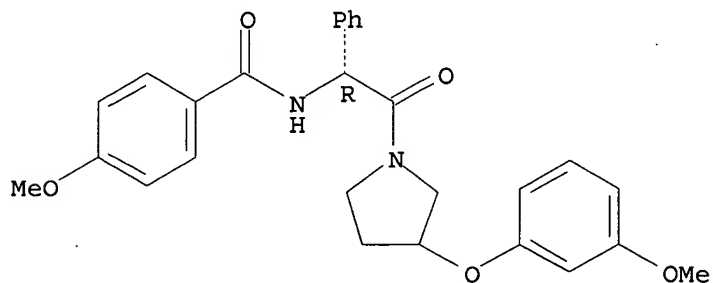


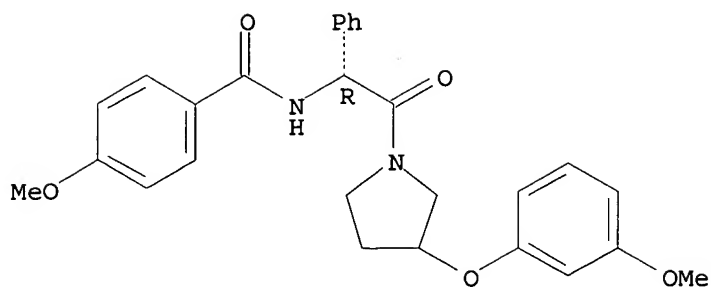
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313487-90-0 REGISTRY
CN Benzamide, 4-methoxy-N-[(1R)-2-[3-(3-methoxyphenoxy)-1-pyrrolidinyl]-2-oxo-1-phenylethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H28 N2 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



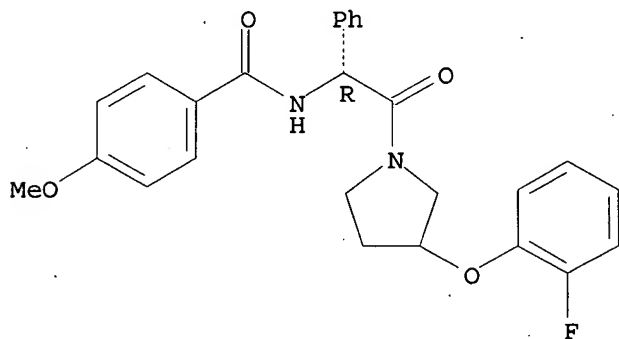


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L3 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 313487-89-7 REGISTRY
CN Benzamide, N-[(1R)-2-[3-(2-fluorophenoxy)-1-pyrrolidinyl]-2-oxo-1-phenylethyl]-4-methoxy- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H25 F N2 O4
SR CA
LC STN Files: CA, CAPLUS.

Absolute stereochemistry.

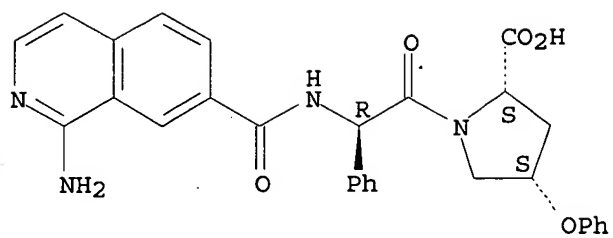


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

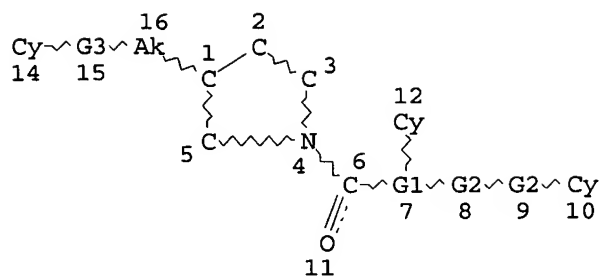
L3 ANSWER 12 OF 12 REGISTRY COPYRIGHT 2003 ACS
RN 221050-61-9 REGISTRY
CN L-Proline, (2R)-N-[(1-amino-7-isoquinolinyl)carbonyl]-2-phenylglycyl-4-phenoxy-, (4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H26 N4 O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1957 TO DATE)



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VAR G2=O/S/C/N
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ENTER (DIS), GRA, NOD, BON OR ?:end
L7  STRUCTURE CREATED

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SAMPLE SCREEN SEARCH COMPLETED - 20619 TO ITERATE

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INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

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0 ANSWERS

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FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH    **COMPLETE**
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PROJECTED ANSWERS:       0 TO      0

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L8          0 SEA SSS SAM L7

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FULL SEARCH INITIATED 14:07:53 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 413103 TO ITERATE

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96.0% PROCESSED  396435 ITERATIONS

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0 ANSWERS

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96.8% PROCESSED  400000 ITERATIONS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.21

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0 ANSWERS

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                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:    413103 TO  413103
PROJECTED ANSWERS:       0 TO      0

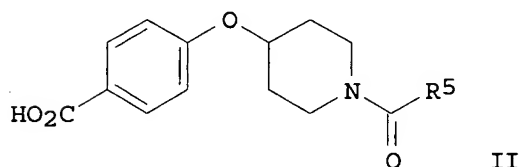
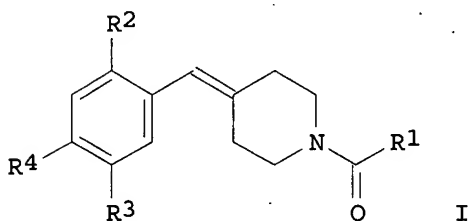
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L9          0 SEA SSS FUL L7

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AN 2002:488375 CAPLUS
 DN 137:216843
 TI Synthesis and Evaluation of 2'-Substituted 4-(4'-Carboxy- or
 4'-carboxymethylbenzylidene)-N-acylpiperidines: Highly Potent and in Vivo
 Active Steroid 5.alpha.-Reductase Type 2 Inhibitors
 AU Picard, Franck; Barassin, Stephan; Mokhtarian, Armand; Hartmann, Rolf W.
 CS Pharmaceutical and Medicinal Chemistry, Saarland University, Saarbruecken,
 D-66041, Germany
 SO Journal of Medicinal Chemistry (2002), 45(16), 3406-3417
 CODEN: JMCMAR; ISSN: 0022-2623
 PB American Chemical Society
 DT Journal
 LA English
 OS CASREACT 137:216843
 GI



AB Sixteen N-acylpiperidines I (R1 = Ph2CH, Ph2CHCH2, dicyclohexylmethyl, 1-adamantyl; R2 = H, F, MeO; R3 = H, HO2C; R4 = H, HO2C, HO2CCH2) and II (R5 = Ph2CH, Ph2N, Me3CO, 1-adamantyl), bearing carboxylic acid moieties, were synthesized and evaluated for inhibition of rat and human steroid 5.alpha.-reductase isoenzymes types 1 and 2. In the dicyclohexylacetyl series (R1 = dicyclohexylmethyl), fluorination in the 2-position of the benzene nucleus, exchange of the carboxy group by a carboxymethyl moiety, and combination of both structural modifications led to highly active inhibitors of the human type 2 isoenzyme [IC50 values: I (R2 = F, R3 = H, R4 = HO2C; (III)], 11 nM; I (R2 = R3 = H, R4 = HO2CCH2), 6 nM; I (R2 = F, R3 = H, R4 = HO2CCH2), 7 nM; finasteride, 5 nM]. In vivo all compds. tested markedly reduced the prostate wts. in castrated testosterone-treated rats. Oral activity was shown for compd. I (R1 = dicyclohexylmethyl, R2 = R3 = H, R4 = HO2C). From the finding that III is active in the rat, although it is a rather poor inhibitor of the rat enzyme and is a strong inhibitor of the human enzyme, it is concluded that it should be highly potent in men.

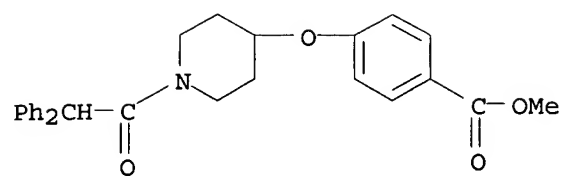
IT 455323-67-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of steroid 5.alpha.-reductase inhibiting acylpiperidines via N-acylation of phenoxypiperidines)

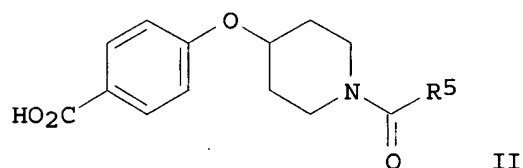
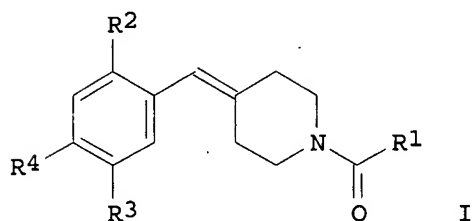
RN 455323-67-8 CAPLUS

CN Benzoic acid, 4-[[1-(diphenylacetyl)-4-piperidinyl]oxy]-, methyl ester (9CI) (CA INDEX NAME)



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 2002:488375 CAPLUS
 DN 137:216843
 TI Synthesis and Evaluation of 2'-Substituted 4-(4'-Carboxy- or
 4'-carboxymethylbenzylidene)-N-acylpiperidines: Highly Potent and in Vivo
 Active Steroid 5.alpha.-Reductase Type 2 Inhibitors
 AU Picard, Franck; Barassin, Stephan; Mokhtarian, Armand; Hartmann, Rolf W.
 CS Pharmaceutical and Medicinal Chemistry, Saarland University, Saarbruecken,
 D-66041, Germany
 SO Journal of Medicinal Chemistry (2002), 45(16), 3406-3417
 CODEN: JMCMAR; ISSN: 0022-2623
 PB American Chemical Society
 DT Journal
 LA English
 OS CASREACT 137:216843
 GI



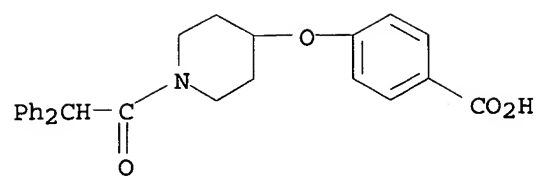
AB Sixteen N-acylpiperidines I (R1 = Ph2CH, Ph2CHCH2, dicyclohexylmethyl, 1-adamantyl; R2 = H, F, MeO; R3 = H, HO2C; R4 = H, HO2C, HO2CCH2) and II (R5 = Ph2CH, Ph2N, Me3CO, 1-adamantyl), bearing carboxylic acid moieties, were synthesized and evaluated for inhibition of rat and human steroid 5.alpha.-reductase isoenzymes types 1 and 2. In the dicyclohexylacetyl series (R1 = dicyclohexylmethyl), fluorination in the 2-position of the benzene nucleus, exchange of the carboxy group by a carboxymethyl moiety, and combination of both structural modifications led to highly active inhibitors of the human type 2 isoenzyme [IC50 values: I [R2 = F, R3 = H, R4 = HO2C; (III)], 11 nM; I (R2 = R3 = H, R4 = HO2CCH2), 6 nM; I (R2 = F, R3 = H, R4 = HO2CCH2), 7 nM; finasteride, 5 nM]. In vivo all compds. tested markedly reduced the prostate wts. in castrated testosterone-treated rats. Oral activity was shown for compd. I (R1 = dicyclohexylmethyl, R2 = R3 = H, R4 = HO2C). From the finding that III is active in the rat, although it is a rather poor inhibitor of the rat enzyme and is a strong inhibitor of the human enzyme, it is concluded that it should be highly potent in men.

IT 455323-72-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (prepn. of steroid 5.alpha.-reductase inhibiting acylpiperidines)

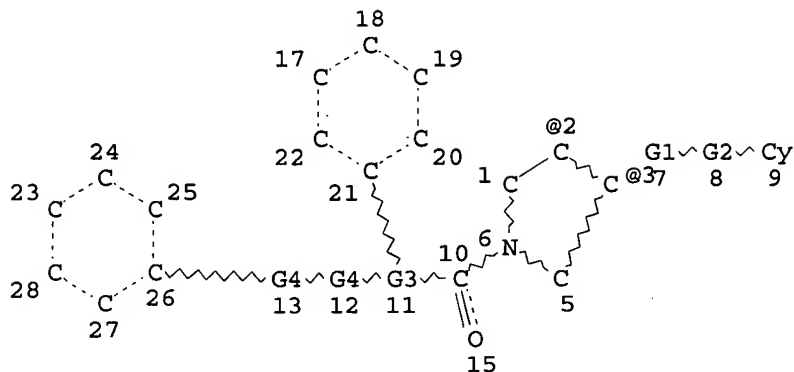
RN 455323-72-5 CAPLUS

CN Benzoic acid, 4-[[1-(diphenylacetyl)-4-piperidinyl]oxy]- (9CI) (CA INDEX NAME)



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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 L14 HAS NO ANSWERS
 L14 STR



VAR G1=2/3
 VAR G2=O/N
 VAR G3=C/N
 VAR G4=C/O/S/N
 NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 GGCAT IS MCY UNS AT 9
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RSPEC 23 21 6
 NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

=> s l14 ful
 FULL SEARCH INITIATED 15:45:39 FILE 'REGISTRY'
 FULL SCREEN SEARCH COMPLETED - 465221 TO ITERATE

86.0% PROCESSED 400000 ITERATIONS
 INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
 SEARCH TIME: 00.00.21

4 ANSWERS

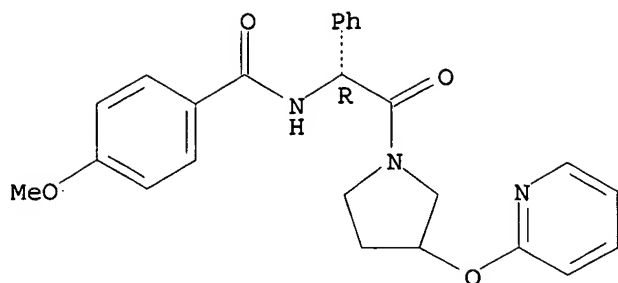
FULL FILE PROJECTIONS: ONLINE **INCOMPLETE**
 BATCH **COMPLETE**
 PROJECTED ITERATIONS: 465221 TO 465221
 PROJECTED ANSWERS: 4 TO 10

L16 4 SEA SSS FUL L14

=> d 1-4

L16 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2003 ACS
 RN 313488-47-0 REGISTRY
 CN Benzamide, 4-methoxy-N-[(1R)-2-oxo-1-phenyl-2-[3-(2-pyridinyloxy)-1-pyrrolidinylethyl]- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C25 H25 N3 O4
 SR CA
 LC STN Files: CA, CAPLUS

Absolute stereochemistry.

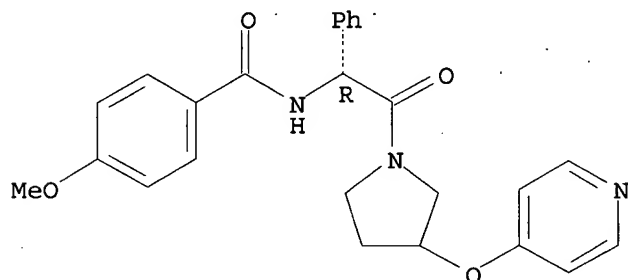


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 313488-44-7 REGISTRY
CN Benzamide, 4-methoxy-N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H25 N3 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

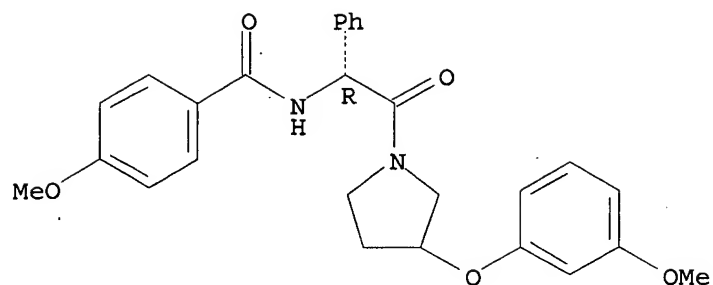


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 313487-90-0 REGISTRY
CN Benzamide, 4-methoxy-N-[(1R)-2-[3-(3-methoxyphenoxy)-1-pyrrolidinyl]-2-oxo-1-phenylethyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H28 N2 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

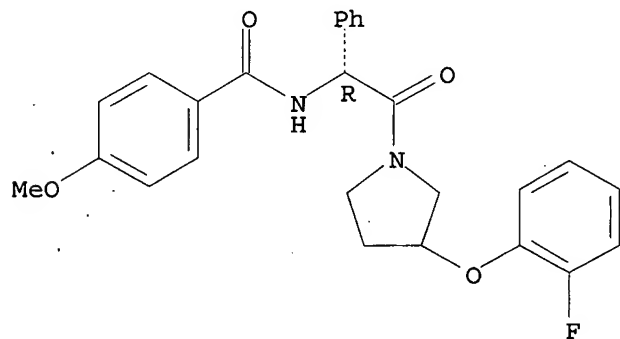


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 313487-89-7 REGISTRY
CN Benzamide, N-[(1R)-2-[[3-(2-fluorophenoxy)-1-pyrrolidinyl]-2-oxo-1-phenylethyl]-4-methoxy- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H25 F N2 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

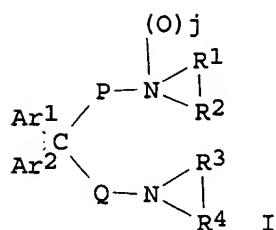


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

AN 2001:228703 CAPLUS
 DN 134:252267
 TI Preparation of diarylalakanediamine derivatives as melanin concentrating hormone (MCH) antagonists
 IN Kato, Kaneyoshi; Mori, Masaaki; Suzuki, Nobuhiro; Shimomura, Yukio; Takekawa, Shiro; Choh, Nobuo
 PA Takeda Chemical Industries, Ltd., Japan
 SO PCT Int. Appl., 284 pp.
 CODEN: PIXXD2
 DT Patent
 LA Japanese
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001021169	A1	20010329	WO 2000-JP6376	20000919
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000073158	A5	20010424	AU 2000-73158	20000919
	JP 2002097138	A2	20020402	JP 2000-288894	20000919
	EP 1219294	A1	20020703	EP 2000-961076	20000919
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
PRAI	JP 1999-266278	A	19990920		
	JP 2000-221055	A	20000717		
	WO 2000-JP6376	W	20000919		
OS	MARPAT 134:252267				
GI					



AB Comps. of general formula [I; wherein Ar1 and Ar2 are each an optionally substituted arom. group; P and Q are each a divalent aliph. hydrocarbon group which may contain ethereal oxygen or sulfur in the carbon chain and may be substituted; R1 and R3 are each (i) hydrogen, (ii) acyl, or (iii) optionally substituted hydrocarbyl; R2 and R4 are each (i) hydrogen, (ii) optionally substituted alkyl, or (iii) optionally substituted alkylcarbonyl; alternatively R1 and R2 or R3 and R4 together with the nitrogen atom adjacent thereto may form a monocyclic or fused nitrogenous heterocyclic group; and j is 0 or 1], salts of the same, or prodrugs thereof are prep'd. These comps. are useful for the treatment of diseases caused by MCH, e.g. obesity (as antiobesity agents) or overeating (as appetite depressants), or for the improvement of emotional disorders or sexual function. Thus, benzyl 2-[(5-hydroxy-2,2-diphenylpentyl)amino]-2-oxoethylcarbamate was brominated by Br and Ph3P in MeCN at room temp. for

1 h to give benzyl 2-[(5-bromo-2,2-diphenylpentyl)amino]-2-oxoethylcarbamate which was dissolved in MeCN, treated with 4-phenylpiperidine and K₂CO₃ in MeCN, and stirred at 40.degree. overnight to give, after purifn. on alumina column chromatog. and conversion into the HCl, benzyl 2-[[2,2-diphenyl-5-(4-phenylpiperidino)pentyl]amino]-2-oxoethylcarbamate hydrochloride (II). II in vitro inhibited the binding of [35S]-guanosine 5'-(.gamma.-thio)triphosphate to human somatostatin-like receptor (SLC-1) with IC₅₀ of 5 nM. Tablet formulations contg. II were described. .

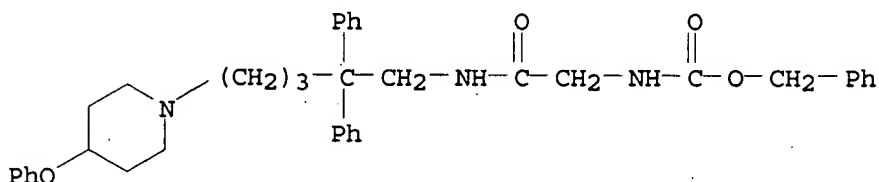
IT 331630-28-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of diarylalkanediamine derivs. as melanin concg. hormone (MCH) antagonists for treating MCH-caused diseases)

RN 331630-28-5 CAPLUS

CN Carbamic acid, [2-oxo-2-[[5-(4-phenoxy-1-piperidinyl)-2,2-diphenylpentyl]amino]ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



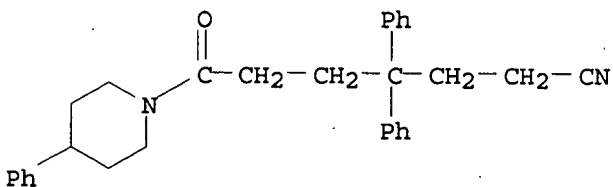
IT 331628-99-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of diarylalkanediamine derivs. as melanin concg. hormone (MCH) antagonists for treating MCH-caused diseases)

RN 331628-99-0 CAPLUS

CN Piperidine, 1-(6-cyano-1-oxo-4,4-diphenylhexyl)-4-phenyl- (9CI) (CA INDEX NAME)



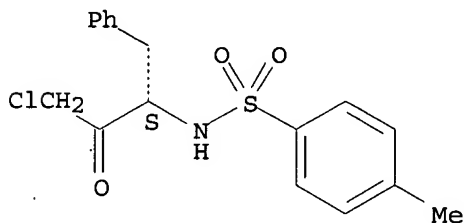
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 1999:685919 CAPLUS
 DN 132:34525
 TI Chloromethyl ketones inhibit interleukin-12 production in mouse
 macrophages stimulated with lipopolysaccharide
 AU Kang, B. Y.; Chung, S. W.; Im, S.-Y.; Hwang, S. Y.; Kim, T. S.
 CS College of Pharmacy and Research Institute of Drug Development, Chonnam
 National University, Kwangju, S. Korea
 SO Immunology Letters (1999), 70(2), 135-138
 CODEN: IMLED6; ISSN: 0165-2478
 PB Elsevier Science Ireland Ltd.
 DT Journal
 LA English
 AB Interleukin-12 (IL-12) plays a pivotal role in the development of T-helper
 type 1 (Th1) immune response, which may be involved in the pathogenesis of
 chronic inflammatory autoimmune disorders. In this study, we investigated
 the effects of N-.alpha.-tosyl-L-phenylalanine chloromethyl ketone (TPCK)
 and N-.alpha.-tosyl-L-lysine chloromethyl ketone (TLCK), serine protease
 inhibitors, on the prodn. of IL-12 from macrophages stimulated with
 lipopolysaccharide (LPS). TPCK and TLCK potently inhibited this
 LPS-induced IL-12 prodn. in a dose-dependent manner. The effect of TPCK
 and TLCK on the IL-12 p40 promoter activation was analyzed by transfecting
 monocytic RAW264.7 cells with p40 promoter-reporter constructs. The
 repressive effect maps to a region in the p40 promoter contg. a binding
 site for NF.kappa.B (p40-.kappa.B). A linker scan mutant of the
 p40-.kappa.B site abrogates the inhibitory effect on the p40 promoter,
 confirming the functional relevance of the NF.kappa.B site. Our results
 show that TPCK and TLCK inhibit NF.kappa.B-mediated IL-12 prodn. in
 macrophages.
 IT 37259-58-8, Serine proteinase
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); BIOL (Biological study)
 (inhibitors; serine proteinase inhibitors inhibit interleukin-12 prodn.
 in mouse macrophages stimulated with lipopolysaccharide)
 RN 37259-58-8 CAPLUS
 CN Proteinase, serine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

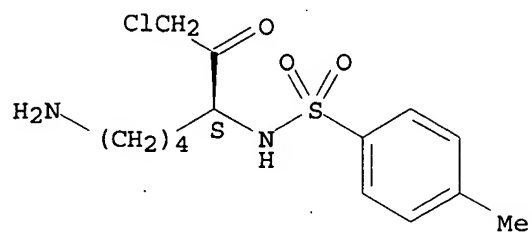
IT 402-71-1, Tpck 2364-87-6, Tlck
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
 (Uses)
 (serine proteinase inhibitors inhibit interleukin-12 prodn. in mouse
 macrophages stimulated with lipopolysaccharide)
 RN 402-71-1 CAPLUS
 CN Benzenesulfonamide, N-[(1S)-3-chloro-2-oxo-1-(phenylmethyl)propyl]-4-
 methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 2364-87-6 CAPLUS
 CN Benzenesulfonamide, N-[(1S)-5-amino-1-(chloroacetyl)pentyl]-4-methyl-
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.

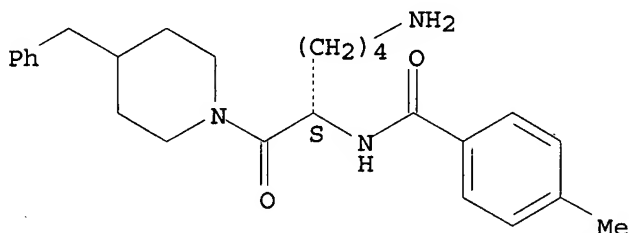


RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 1986:497950 CAPLUS
 DN 105:97950
 TI Lysine derivative and proteinase inhibitor
 IN Okamoto, Shosuke; Okada, Yoshio; Okunomiya, Akiko; Naito, Taketoshi;
 Yamada, Morihiko; Kimura, Yoshio; Katsuura, Yasuhiro; Suzuki, Hiroshi;
 Ohno, Norio; Seki, Yumi
 PA Showa Denko K. K., Japan
 SO Eur. Pat. Appl., 86 pp.
 CODEN: EPXXDW
 DT Patent
 LA English
 FAN. CNT 1

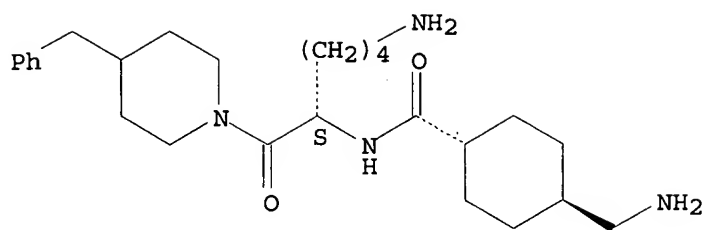
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 183271	A2	19860604	EP 1985-115142	19851129
	EP 183271	A3	19870520		
	EP 183271	B1	19900516		
	R: CH, DE, FR, GB, LI, SE				
	JP 61130268	A2	19860618	JP 1984-251985	19841130
	JP 61189255	A2	19860822	JP 1985-26556	19850215
	JP 61218565	A2	19860929	JP 1985-56153	19850322
	JP 62005945	A2	19870112	JP 1985-143852	19850702
PRAI	JP 1984-251985		19841130		
	JP 1985-26556		19850215		
	JP 1985-56153		19850322		
	JP 1985-143852		19850702		
AB	Lysines R1Z1-Lys-R2 (R1 = carbocyclic or heterocyclic aryl; Z1 = SO2, CO; R2 = NH2, substituted amino), which were prepd., showed plasmin inhibition activity. N2-(p-Toluenesulfonyl)-L-lysine 4-benzylpiperidide was prepd. from N6-(benzyloxycarbonyl)lysine in a series of reactions.				
IT	103880-75-7P 103880-79-1P 103880-80-4P 103880-81-5P 103880-82-6P RL: SPN (Synthetic preparation); PREP (Preparation) (prepn. of, as plasmin inhibitor)				
RN	103880-75-7 CAPLUS				
CN	Benzamide, N-[5-amino-1-[[4-(phenylmethyl)-1-piperidinyl]carbonyl]pentyl]- 4-methyl-, (S)- (9CI) (CA INDEX NAME)				

Absolute stereochemistry.



RN 103880-79-1 CAPLUS
 CN Cyclohexanecarboxamide, 4-(aminomethyl)-N-[5-amino-1-[[4-(phenylmethyl)-1-piperidinyl]carbonyl]pentyl]-, [1(S)-trans]- (9CI) (CA INDEX NAME)

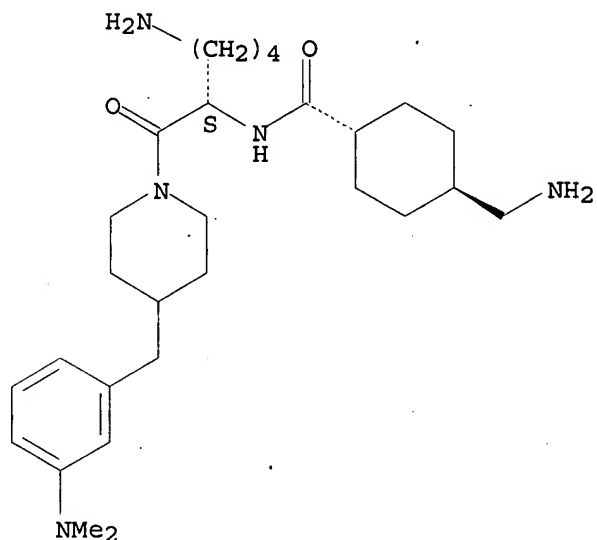
Absolute stereochemistry.



RN 103880-80-4 CAPLUS

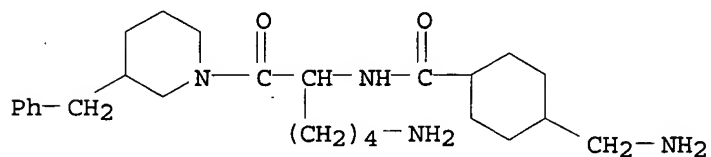
CN Cyclohexanecarboxamide, N-[5-amino-1-[[4-[[3-(dimethylamino)phenyl]methyl]-1-piperidinyl]carbonyl]pentyl]-4-(aminomethyl)-, [1(S)-trans]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



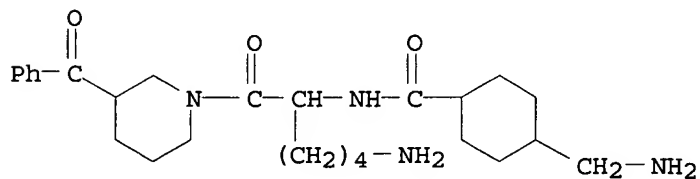
RN 103880-81-5 CAPLUS

CN Cyclohexanecarboxamide, 4-(aminomethyl)-N-[5-amino-1-[[3-(phenylmethyl)-1-piperidinyl]carbonyl]pentyl]- (9CI) (CA INDEX NAME)



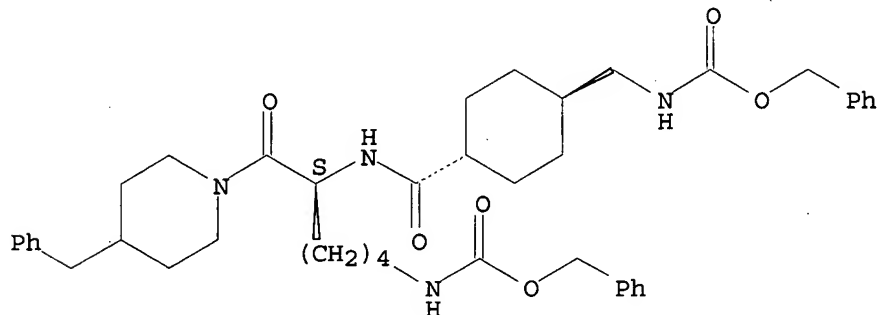
RN 103880-82-6 CAPLUS

CN Cyclohexanecarboxamide, N-[5-amino-1-[[3-benzoyl-1-piperidinyl]carbonyl]pentyl]-4-(aminomethyl)- (9CI) (CA INDEX NAME)



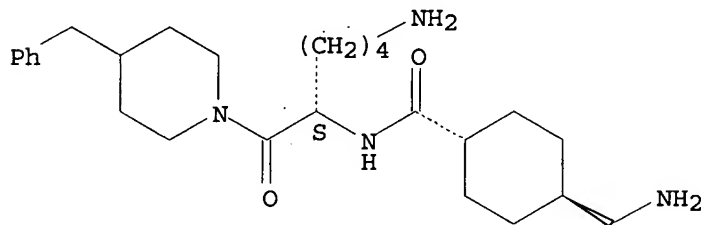
AN 1992:79127 CAPLUS
 DN 116:79127
 TI Development of active center-directed inhibitors against plasmin
 AU Teno, Naoki; Wanaka, Keiko; Okada, Yoshio; Tsuda, Yuko; Okamoto, Utako; Hijikata-Okunomiya, Akiko; Naito, Taketoshi; Okamoto, Shosuke
 CS Fac. Pharm. Sci., Kobe-Gakuin Univ., Kobe, 651-21, Japan
 SO Chemical & Pharmaceutical Bulletin (1991), 39(9), 2340-6
 CODEN: CPBTAL; ISSN: 0009-2363
 DT Journal
 LA English
 AB Active center-directed inhibitors of plasmin were designed based on the structure of specific substrates of plasmin and then synthesized. Their effects on plasmin were examd. and the structure-inhibitory activity relationship was studied. N2-trans-4-Aminomethylcyclohexanecarbonyllysine 4-benzoylanilide (Tra-Lys-BZA) inhibited plasmin activities toward S-2251 and fibrin with IC50 values of 15 and 6.1 .mu.M, resp. and N2-trans-4-aminomethylcyclohexanecarbonyllysine 4-benzylpiperidine amide (Tra-Lys-BPP) did not show any detectable inhibitory activity. Moreover, it was revealed that Tra-Lys-4-methoxycarbonylanilide inhibited plasma kallikrein more potently than plasmin.
 IT 138848-85-8P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. and deprotection of)
 RN 138848-85-8 CAPLUS
 CN Carbamic acid, [6-oxo-5-[[[4-[[[(phenylmethoxy) carbonyl] amino] methyl] cyclohexyl] carbonyl] amino]-6-[4-(phenylmethyl)-1-piperidinyl]hexyl]-, phenylmethyl ester, [1(S)-trans]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 103880-79-1P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and plasmin inhibition by)
 RN 103880-79-1 CAPLUS
 CN Cyclohexanecarboxamide, 4-(aminomethyl)-N-[5-amino-1-[[4-(phenylmethyl)-1-piperidinyl]carbonyl]pentyl]-, [1(S)-trans]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



c-myc mRNA and up-regulation of c-fos and egr-1 mRNA and protein, which normally occur during TPA-induced differentiation, were not affected by inclusion of the **protease inhibitors**. These data indicate that **serine proteases** specifically mediate many of the phenotypic aspects of TPA-induced monocytic differentiation, but are not involved with the induction or repression of differentiation-sensitive transcription factors, and suggest that **serine protease** activity is required for intracellular processing of CD11b. (c) 2000 Academic Press.

ST **serine protease** role phorbol ester induced HL60 cell differentiation; CD11b processing phorbol ester induced HL60 cell differentiation

L10 ANSWER 4 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1999:685919 CAPLUS

DN 132:34525

TI Chloromethyl ketones inhibit interleukin-12 production in mouse macrophages stimulated with lipopolysaccharide

AU Kang, B. Y.; Chung, S. W.; Im, S.-Y.; Hwang, S. Y.; Kim, T. S.

CS College of Pharmacy and Research Institute of Drug Development, Chonnam National University, Kwangju, S. Korea

SO Immunology Letters (1999), 70(2), 135-138

CODEN: IMLED6; ISSN: 0165-2478

PB Elsevier Science Ireland Ltd.

DT Journal

LA English

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Interleukin-12 (IL-12) plays a pivotal role in the development of T-helper type 1 (Th1) immune response, which may be involved in the pathogenesis of chronic inflammatory autoimmune disorders. In this study, we investigated the effects of N-.alpha.-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK) and N-.alpha.-tosyl-L-**lysine** chloromethyl ketone (TLCK), **serine protease inhibitors**, on the prodn. of IL-12 from macrophages stimulated with lipopolysaccharide (LPS). TPCK and TLCK potently **inhibited** this LPS-induced IL-12 prodn. in a dose-dependent manner. The effect of TPCK and TLCK on the IL-12 p40 promoter activation was analyzed by transfecting monocytic RAW264.7 cells with p40 promoter-reporter constructs. The repressive effect maps to a region in the p40 promoter contg. a binding site for NF.kappa.B (p40-.kappa.B). A linker scan mutant of the p40-.kappa.B site abrogates the **inhibitory** effect on the p40 promoter, confirming the functional relevance of the NF.kappa.B site. Our results show that TPCK and TLCK **inhibit** NF.kappa.B-mediated IL-12 prodn. in macrophages.

L10 ANSWER 5 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1999:423946 CAPLUS

DN 131:193814

TI **Serine protease inhibitor** TPCK prevents

Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells

AU Huang, Ying; Sheikh, M. Saeed; Fornace, Albert J, Jr.; Holbrook, Nikki J.

CS Gene Expression and Aging Section, Laboratory of Biological Chemistry, National Institute on Aging, Baltimore, MD, 21224, USA

SO Oncogene (1999), 18(23), 3431-3439

CODEN: ONCNES; ISSN: 0950-9232

PB Stockton Press

DT Journal

LA English

RE.CNT 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Serine protease inhibitor** TPCK prevents

Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells

AB The mechanism of Taxol-induced apoptosis was investigated in MCF-7 human breast carcinoma cells. Taxol-induced apoptosis was assocd. with phosphorylation of both c-Raf-1 and Bcl-2 and activation of ERK and JNK MAP kinases. The **serine protease inhibitor** N-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK) effectively blocked apoptosis, but N-p-tosyl-L-**lysine** chloromethyl ketone (TLCK), another **serine protease inhibitor**, was without effect. TPCK treatment also prevented phosphorylation of c-Raf-1 and Bcl-2 in response to Taxol treatment. The **serine protease inhibitor** did not alter JNK activity, but it enhanced Taxol-induced activation of ERK1/2. Treatment of cells with the **inhibitor** of MEK activation, PD98059, prevented Taxol-induced ERK activation both in the presence and absence of TPCK, but did not influence survival of either Taxol- or Taxol plus TPCK-treated cells. In addn., PD98059 had no effect on c-Raf-1 or Bcl-2 phosphorylation. Thus, while the Taxol-induced phosphorylations of c-Raf-1 and Bcl-2 proteins appear to be coupled, these events can be disassocd. from ERK1/2 activation. In summary, these findings suggest that phosphorylation of c-Raf-1 and Bcl-2, but not ERK1/2, are important signaling events in Taxol-induced apoptosis of MCF-7 breast cancer cells and that a TPCK **inhibitable protease(s)** is required for these processes.

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(bcl-2; **serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

IT Mammary gland
Mammary gland
(carcinoma, **inhibitors**; **serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

IT Antitumor agents
(mammary gland carcinoma; **serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

IT Apoptosis
Phosphorylation, biological
(**serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

IT 33069-62-4, Taxol
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

IT 139691-76-2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**serine protease inhibitor** TPCK prevents Taxol-induced cell death and blocks c-Raf-1 and Bcl-2 phosphorylation in human breast carcinoma cells)

L10 ANSWER 6 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1999:360059 CAPLUS

DN 131:208734

TI **Inhibition** of drug-induced DNA fragmentation, but not cell death, of glioma cells by non-caspase **protease inhibitors**

AU Eitel, Katrin; Wagenknecht, Bettina; Weller, Michael
CS Department of Neurology, Laboratory of Molecular Neuro-Oncology, School of
Medicine, University of Tübingen, Tübingen, 72076, Germany
SO Cancer Letters (Shannon, Ireland) (1999), 142(1), 11-16
CODEN: CALEDQ; ISSN: 0304-3835
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Inhibition** of drug-induced DNA fragmentation, but not cell
death, of glioma cells by non-caspase **protease**
inhibitors

AB The role of non-caspase **protease** activation in drug-induced cell
death of glioma cells was examd. Neither calpain **inhibitors** I
or II, phenylmethylsulfonyl fluoride (PMSF), N.alpha. -p-tosyl-l-
lysine chloromethyl ketone (TLCK), N-tosyl-l-**phenylalanine**
chloromethyl ketone (TPCK), E64, leupeptin nor pepstatin **inhibit**
the cytotoxicity of vincristine, cisplatin, doxorubicin, cytarabine,
camptothecin, BCNU or VM26 in two malignant glioma cell lines, T98G and
LN-229. However, DNA fragmentation induced by VM26 is **inhibited**
by calpain **inhibitor** I, PMSF, TLCK and TPCK, and that induced by
camptothecin by calpain **inhibitors** I and II and TPCK. Moreover,
protease inhibitors fail to abrogate CD95 ligand-induced
apoptosis even though DNA fragmentation is attenuated by calpain
inhibitor II and TPCK. Thus, non-caspase **protease**
activation is not required for drug-induced apoptosis of glioma cells.
Protease inhibitor-mediated inhibition of DNA
fragmentation operates downstream of the commitment point for cell death.

ST glioma apoptosis **protease inhibitor** antitumor
interaction; DNA fragmentation signaling glioma **protease**
anticancer

IT DNA
(fragmentation; **inhibition** of drug-induced DNA fragmentation,
but not apoptosis, of glioma cells by non-caspase **protease**
inhibitors)

IT Neuroglia
Neuroglia
(glioma, **inhibitors**; **inhibition** of drug-induced DNA
fragmentation, but not apoptosis, of glioma cells by non-caspase
protease inhibitors)

IT Antitumor agents
(glioma; **inhibition** of drug-induced DNA fragmentation, but
not apoptosis, of glioma cells by non-caspase **protease**
inhibitors)

IT Apoptosis
Drug interactions
Signal transduction, biological
(**inhibition** of drug-induced DNA fragmentation, but not
apoptosis, of glioma cells by non-caspase **protease**
inhibitors)

IT 78990-62-2, Calpain
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(I and II; **inhibition** of drug-induced DNA fragmentation, but
not apoptosis, of glioma cells by non-caspase **protease**
inhibitors)

IT 57-22-7, Vincristine 147-94-4, Cytarabine 154-93-8, BCNU 7689-03-4,
Camptothecin 15663-27-1, Cisplatin 23214-92-8, Doxorubicin
29767-20-2, VM26
RL: BAC (Biological activity or effector, except adverse); BPR (Biological
process); BSU (Biological study, unclassified); THU (Therapeutic use);
BIOL (Biological study); PROC (Process); USES (Uses)

(inhibition of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase **protease inhibitors**)

IT 329-98-6, Phenylmethylsulfonyl fluoride 402-71-1 2364-87-6
26305-03-3 37259-58-8, **Serine protease** 37353-41-6,
Cysteine proteinase 55123-66-5, Leupeptin 66701-25-5, E64
78169-47-8, **Aspartic protease**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(inhibition of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase **protease inhibitors**)

IT 9001-92-7, **Protease**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(trypsin-like and Chymotrypsin-like; **inhibition of drug-induced DNA fragmentation, but not apoptosis, of glioma cells by non-caspase protease inhibitors**)

L10 ANSWER 7 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1999:158902 CAPLUS

DN 130:294043

TI Inflorescence bud protease(s) against dehydrin-like inflorescence bud proteins of Pistacia vera

AU Peri, Irena; Matusova, Radoslava; Smirnoff, Patricia; Birk, Yehudith; Golan-Goldhirsh, Avi

CS Desert Plant Biotechnology Laboratory, The Jacob Blaustein Institute for Desert Research, The Albert Katz Center for Desert Agrobiological, Ben-Gurion University of the Negev, 84990, Israel

SO Plant Physiology and Biochemistry (Paris) (1999), 37(1), 51-56
CODEN: PPBIEX; ISSN: 0981-9428

PB Editions Scientifiques et Medicales Elsevier

DT Journal

LA English

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A proteolytic activity extd. from Pistacia vera L. (pistachio) inflorescence buds, found in male and female tissues is reported. The proteolytic activity reaches a peak at the beginning of bud opening and flowering and is directed against inflorescence bud dehydrin-like proteins of pistachio, IBP32 and IBP27. The effect of **protease inhibitors** indicated that the **protease(s)** belong to a **serine-protease**-like family and are not cysteine, acid or metallo-**proteases**. The proteolytic activity was strongly **inhibited** by N.alpha.-p-tosyl-L-lysine chloromethyl ketone and to a lesser extent by N-tosyl-L-**phenylalanine** chloromethyl ketone, suggesting mainly trypsin-like specificity or broader **serine-protease** specificity. It is suggested that the proteolytic activity is important in the mobilization of nitrogen reserves stored in the bud storage proteins during dormancy to support the fast-developing inflorescence in spring after bud dormancy break.

IT 37259-58-8, **Serine proteinase**

RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)

(inflorescence bud **protease(s)** against dehydrin-like inflorescence bud proteins of Pistacia vera)

L10 ANSWER 8 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1997:179985 CAPLUS

DN 126:181000

TI Differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents.

[Erratum to document cited in CA125:316457

AU Lotem, Joseph; Sachs, Leo
CS Dep. Mol. Genetics, Weizmann Inst. Sci., Rehovot, 76100, Israel
SO Proceedings of the National Academy of Sciences of the United States of
America (1997), 94(4), 1603
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
TI Differential suppression by **protease inhibitors** and
cytokines of apoptosis induced by wild-type p53 and cytotoxic agents.
[Erratum to document cited in CA125:316457
AB The authors correct the second sentence of their original abstr. to read
as follows. Apoptosis was also suppressed by the **serine** and
cysteine **protease inhibitor** N-tosyl-L-
phenylalanine chloromethylketone (TPCK), but not by other
serine or cysteine **protease inhibitors**
including N.alpha.-p-tosyl-L-lysine chloromethylketone (TLCK),
E64, pepstatin A, or chymostatin.
ST erratum apoptosis **protease inhibitor** cytokine gene;
apoptosis **protease inhibitor** cytokine gene erratum;
protease inhibitor cytokine gene p53 erratum; cytotoxic
agent apoptosis **protease inhibitor** erratum; agent
apoptosis **protease inhibitor** cytokine erratum
IT Gene, animal
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(TP53; differential suppression by **protease**
inhibitors and cytokines of apoptosis induced by wild-type p53
and cytotoxic agents (Erratum))
IT Apoptosis
Cytotoxic agents
(differential suppression by **protease inhibitors**
and cytokines of apoptosis induced by wild-type p53 and cytotoxic
agents (Erratum))
IT Interleukin 3
Interleukin 6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(differential suppression by **protease inhibitors**
and cytokines of apoptosis induced by wild-type p53 and cytotoxic
agents (Erratum))
IT Hematopoietic precursor cell
(myeloid; differential suppression by **protease**
inhibitors and cytokines of apoptosis induced by wild-type p53
and cytotoxic agents (Erratum))
IT Thymus gland
(thymocyte; differential suppression by **protease**
inhibitors and cytokines of apoptosis induced by wild-type p53
and cytotoxic agents (Erratum))
IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(.gamma.; differential suppression by **protease**
inhibitors and cytokines of apoptosis induced by wild-type p53
and cytotoxic agents (Erratum))
IT 9047-22-7, Cathepsin B 60616-82-2, Cathepsin L 122191-40-6,
Interleukin-1.beta.-converting enzyme
RL: BAC (Biological activity or effector, except adverse); BPR (Biological
process); BSU (Biological study, unclassified); BIOL (Biological study);
PROC (Process)

(differential suppression by **protease inhibitors**
and cytokines of apoptosis induced by wild-type p53 and cytotoxic
agents (Erratum))

IT 50-02-2, Dexamethasone 57-22-7, Vincristine 66-81-9, Cycloheximide
402-71-1 2364-87-6 9076-44-2, Chymostatin 23214-92-8 25013-16-5,
BHA 26305-03-3, Pepstatin A 60525-17-9 66701-25-5, E64 83869-56-1,
GM-CSF 143180-74-9, Granzyme B 161401-82-7 183284-21-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)

(differential suppression by **protease inhibitors**
and cytokines of apoptosis induced by wild-type p53 and cytotoxic
agents (Erratum))

L10 ANSWER 9 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1996:665142 CAPLUS

DN 125:316457

TI Differential suppression by **protease inhibitors** and
cytokines of apoptosis induced by wild-type p53 and cytotoxic agents

AU Lotem, Joseph; Sachs, Leo

CS Dep. Mol. Genetics, Weizmann Inst. Sci., Rehovot, 76100, Israel

SO Proceedings of the National Academy of Sciences of the United States of
America (1996), 93(22), 12507-12512

CODEN: PNASA6; ISSN: 0027-8424

PB National Academy of Sciences

DT Journal

LA English

TI Differential suppression by **protease inhibitors** and
cytokines of apoptosis induced by wild-type p53 and cytotoxic agents

AB Apoptosis induced in myeloid leukemic cells by wild-type p53 was
suppressed by different cleavage-site directed **protease
inhibitors**, which **inhibit** interleukin-1.beta.-converting
enzyme-like, granzyme B and cathepsins B and L **proteases**.
Apoptosis was also suppressed by the **serine** and cysteine
protease inhibitor N-tosyl-L-phenylalanine
chloromethylketone (TPCK), E64, but not by other **serine** or
cysteine **protease inhibitors** including
N.alpha.-p-tosyl-L-lysine chloromethylketone (TLCK), E64,
pepstatin A, or chymostatin. **Protease inhibitors**
suppressed induction of apoptosis by .gamma.-irradn. and cycloheximide but
not by doxorubicin, vincristine, or withdrawal of interleukin 3 from
interleukin 3-dependent 32D non-malignant myeloid cells. Induction of
apoptosis in normal thymocytes by .gamma.-irradn. or dexamethasone was
also suppressed by the cleavage-site directed **protease
inhibitors**, but in contrast to the myeloid leukemic cells
apoptosis in thymocytes was suppressed by TLCK but not by TPCK. The
results indicate that (i) **inhibitors** of interleukin-1.beta.-
converting enzyme-like **proteases** and some other **protease
inhibitors** suppressed induction of apoptosis by wild-type p53 and
certain p53-independent pathways of apoptosis; (ii) the **protease
inhibitors** together with the cytokines interleukin 6 and
interferon-.gamma. or the antioxidant butylated hydroxyanisole gave a
cooperative protection against apoptosis; (iii) these **protease
inhibitors** did not suppress induction of apoptosis by some
cytotoxic agents or by viability-factor withdrawal from 32D cells, whereas
these pathways of apoptosis were suppressed by cytokines; (i.v.) there are
cell type differences in the **proteases** involved in apoptosis;
and (v) there are multiple pathways leading to apoptosis that can be
selectively induced and suppressed by different agents.

ST apoptosis **protease inhibitor** cytokine gene p53;

cytotoxic agent apoptosis **protease inhibitor** cytokine

IT Apoptosis

Cytotoxic agents

(differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Gene, animal
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (TP53, differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Lymphokines and Cytokines
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (interleukin 3, differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Lymphokines and Cytokines
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (interleukin 6, differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Hematopoietic precursor cell
 (myeloid, differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Thymus gland
 (thymocyte, differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT Interferons
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (.gamma., differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT 9047-22-7, Cathepsin B 60616-82-2, Cathepsin L 122191-40-6, Interleukin-1.beta.-converting enzyme
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

IT 50-02-2, Dexamethasone 57-22-7, Vincristine 66-81-9, Cycloheximide 402-71-1 2364-87-6, N.alpha.-p-Tosyl-L-lysine chloromethylketone 9076-44-2, Chymostatin 23214-92-8, Doxorubicin 25013-16-5, BHA 26305-03-3, Pepstatin A 60525-17-9 66701-25-5, E64 83869-56-1, GM-CSF 143180-74-9, Granzyme B 161401-82-7 183284-21-1
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (differential suppression by **protease inhibitors** and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents)

L10 ANSWER 10 OF 29 CAPLUS COPYRIGHT 2003 ACS
 AN 1996:482438 CAPLUS
 DN 125:163645
 TI Partial characterization of protease activity in the midgut of Helicoverpa armigera larvae

AU Wang, Chenzhu; Qin, Junde
 CS Institute Zoology, Academia Sinica, Beijing, 100080, Peop. Rep. China
 SO Kunchong Xuebao (1996), 39(1), 7-14
 CODEN: KCHPA2; ISSN: 0454-6296

PB Kexue
 DT Journal
 LA Chinese

AB The activities of three serine **proteases** in the midgut of *Helicoverpa armigera* larvae were partially characterized. The enzymes were an active alk. trypsin-like enzyme with maximal hydrolysis of benzoyl arginine p-nitroaniline at pH 10.50 or higher; a weak alk. trypsin-like enzyme with maximal hydrolysis of tosyl-L-arginine Me ester at pH 8.50-9.00; and a chymotrypsin-like enzyme with maximal hydrolysis of benzoyl-L-tyrosine Et ester at pH 8.50-9.00. Total proteolysis, measured by using azocasein, had a maximal activity at pH 10.50 or higher. Ca^{2+} had no activation effect on larval **proteases**, but Mg^{2+} activated the weak alk. trypsin-like enzyme. The **inhibition** with Ph Me sulfonyl fluoride and tosyl-L-**lysine** chloromethyl ketone to the weak alk. trypsin-like enzyme activity was greater than that to the active alk. trypsin-like enzyme activity. The tosyl-L-**phenylalanine** chloromethyl ketone was not only the **inhibitor** of the chymotrypsin-like enzyme, but also the activator of the weak alk. trypsin-like enzyme. Comparison between the insect **protease** and bovine counterpart **protease** revealed difference in **inhibitor** sensitivity.

ST *Helicoverpa armigera* **protease** activator **inhibitor**
 IT *Heliothis zea*
 (serine **proteases** of midgut of *Helicoverpa armigera* larvae response to soybean trypsin **inhibitor**)

IT Digestive tract
 (midgut, serine **proteases** of midgut of *Helicoverpa armigera* larvae response to soybean trypsin **inhibitor**)

IT 9002-07-7, Trypsin 9004-07-3, Chymotrypsin 37259-58-8, **Serine protease**
 RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
 (serine **proteases** of midgut of *Helicoverpa armigera* larvae)

IT 9078-38-0, Soybean trypsin **inhibitor**
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (serine **proteases** of midgut of *Helicoverpa armigera* larvae response to soybean trypsin **inhibitor**)

L10 ANSWER 11 OF 29 CAPLUS COPYRIGHT 2003 ACS
 AN 1996:277183 CAPLUS
 DN 124:335473

TI Antiproteases attenuate the release of neutrophil chemotactic activity from bronchial epithelial cells induced by smoke

AU Koyama, Sekiya; Rennard, Stephen I.; Leikauf, George D.; Ertl, Ronald F.; Robbins, Richard A.
 CS School Medicine, Shinshu University, Matsumoto, Japan
 SO Experimental Lung Research (1996), 22(1), 1-19
 CODEN: EXLRDA; ISSN: 0190-2148

PB Taylor & Francis
 DT Journal
 LA English

AB The released neutrophil chemotactic activity (NCA) from bronchial epithelial cells (BECs) in response to smoke ext. was evaluated by reverse-phase, high-performance liq. chromatog. (RP-HPLC) and the involvement of proteolytic activity was assessed for the release of NCA from BECs. Smoke ext. stimulated the release of NCA (55.3 ± 5.2 us. 17.3 ± 4.1 cells per high-power field [HPF], $p < .001$). The released activity detd. by RP-HPLC anal. was 15-hydroxyeicosatetraenoic acid and

leukotriene B4. Several structurally and functionally different **serine protease inhibitors**, including .alpha.-1-**protease inhibitor** (.alpha.-1-PI), chloromethyl ketone (CK) derivs., N-tosyl-L-lysine CK (TLCK), methoxysuccinyl-Ala-Ala-Pro-Val CK (SPCK), N-.alpha.-tosyl-L-phenylalanine CK (TPCK), and N-.alpha.-p-tosyl-L-arginine Me ester hydrochloride (TAME), attenuated the release of NCA (p < .01) in a dose-dependent fashion. Leupeptin, a cysteine **protease inhibitor**, has only a small effect on the release of NCA (p < .05), and phosphoramidon, a neutral endopeptidase **inhibitor**, had no effect. The measurement of proteolytic enzyme activity using synthetic substrate S-2288 revealed that smoke ext. significantly (p < .05) augmented the **serine protease** activity in BEC layers. Culture supernatant fluids and cell lysates of BECs in response to smoke ext. solubilized 14C-labeled casein. These results suggest that BECs may release lipxygenase-derived NCA in response to smoke ext. and that the release of NCA may involve the activation of proteolytic activity of BECs which was **inhibited by serine protease inhibitors**.

IT 37259-58-8, **Serine protease** 71160-24-2, Leukotriene B4 73180-00-4, 15-Hydroxyeicosatetraenoic acid
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (effect of cigarette smoke on neutrophil chemotactic activity and proteases of bronchial epithelial cells)

L10 ANSWER 12 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1996:153397 CAPLUS

DN 124:203102

TI Preparation of peptide containing proline phosphonate derivatives as **inhibitors of serine proteases**

IN Powers, James C.; Boduszek, Bogdan; Oleksyszyn, Jozef

PA Georgia Tech. Research Corp., USA

SO PCT Int. Appl., 39 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9529691	A1	19951109	WO 1995-US5345	19950428

W: CA, JP, MX

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

US 5543396	A	19960806	US 1994-234181	19940428
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PRAI US 1994-234181 19940428

OS MARPAT 124:203102

TI Preparation of peptide containing proline phosphonate derivatives as **inhibitors of serine proteases**

AB Peptidyl derivs. of diesters of .alpha.-aminoalkylphosphonic acids, particularly those with proline or related structures, [I and II; Z, Z1 = C1-6 perfluoroalkyl, (un)substituted Ph; X = a single bond, CH2, CH2CH2, (CH2)3, (CH2)4, Y, CH2Y, YCH2, (H,H); Y = O, S; AA = H, PhCH2O2C, H2NCHRCO (wherein R = C1-6 alkyl optionally fluorinated), .beta.-alanine, glycine, .epsilon.-aminocaproic acid, sarcosine, side chain (un)blocked L-, D-, or DL-.alpha.-amino acid selected from the group consisting of alanine, leucine, isoleucine, proline, methionine, methionine sulfoxide, **phenylalanine**, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, **lysine**, arginine, histidine, phenylglycine, and etc.], useful for **inhibiting serine proteases** with chymotrypsin-like, trypsin-like, elastase-like, and dipeptidyl peptidase IV specificity and their roles as anti-inflammatory agents, anticoagulants, anti-tumor agents, and anti-AIDS agents, are prepd. Thus, to 0.36 g Boc-D-Phe-Pro-OH

in 2 mL dry DMF at 0.degree., 0.17 g N,N'-dicyclohexylcarbodiimide was added. After stirring the mixt. for 1 h, 0.45 g di-Ph amino(4-amidinophenyl)methanephosphonate dihydrochloride was added the soln. was stirred for 48 h to give di-Ph N-(N-tert-butoxycarbonyl-D-phenylalanyl-L-prolyl)amino(4-amidinophenyl)methanephosphonate hydrochloride. H-Ala-ProP(OC6H4Cl-4)2.HCl and H-Ala-PipP(OC6H4Cl-4)2.HCl in vitro at 0.12 mM **inhibited** human placenta dipeptidylpeptidase IV (DPP-IV) at 0 and 88% after 2 min, resp., and 88 and 100%, resp., after 30 min.

- ST peptide phosphonate prepn **inhibitor serine protease**; proline phosphonate contg peptide prepn; antiinflammatory peptide phosphonate; anticoagulant peptide phosphonate; antitumor peptide phosphonate; AIDS treatment peptide phosphonate; dipeptidylpeptidase IV **inhibitor**; aminoalkylphosphonate ester
- IT peptide **serine protease inhibitor**
- IT Inflammation **inhibitors**
Neoplasm **inhibitors**
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of serine **proteases** for therapeutics)
- IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of serine **proteases** for therapeutics)
- IT Acquired immune deficiency syndrome
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of serine **proteases** for treating AIDS)
- IT 82818-44-8P 122299-42-7P 122299-43-8P 122299-44-9P 130699-14-8P
130699-15-9P 130699-16-0P 130699-22-8P 130727-19-4P 130727-20-7P
130727-21-8P 140668-71-9P 174298-04-5P 174298-05-6P 174298-06-7P
174298-07-8P 174298-08-9P 174298-09-0P 174298-10-3P 174298-11-4P
174298-12-5P 174298-13-6P 174298-14-7P 174298-15-8P 174298-16-9P
174298-17-0P 174298-18-1P 174298-19-2P 174298-20-5P 174298-21-6P
174298-22-7P 174298-23-8P 174298-25-0P 174298-26-1P 174298-27-2P
174298-28-3P 174298-29-4P 174298-30-7P 174298-31-8P 174298-32-9P
174298-33-0P 174298-34-1P 174298-35-2P 174298-36-3P 174298-37-4P
174298-38-5P 174298-39-6P 174298-40-9P 174298-41-0P 174298-42-1P
174298-43-2P 174391-77-6P 174391-78-7P 174391-79-8P 174391-80-1P
174391-81-2P 174391-82-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of serine **proteases** for therapeutics)
- IT 37259-58-8, **Serine protease** 54249-88-6,
Dipeptidylpeptidase IV
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. of peptide contg. proline phosphonate derivs. as **inhibitors** of **serine proteases** for therapeutics)
- IT 75-89-8, 2,2,2-Trifluoroethanol 78-84-2, Isobutyraldehyde 101-02-0,
Triphenyl phosphite 105-07-7, 4-Cyanobenzaldehyde 106-48-9,
4-Chlorophenol 371-41-5, 4-Fluorophenol 405-39-0 621-84-1, Benzyl
carbamate 1142-20-7 1148-11-4 1149-26-4 1161-13-3 4712-55-4,
Diphenyl phosphite 7719-12-2, Phosphorus trichloride 13734-41-3
16012-70-7 18942-49-9 27879-53-4, 2,3,4,5-Tetrahydropyridine trimer
38675-10-4 54564-48-6, 1-Pyrroline trimer 65164-80-9 72252-95-0
73270-42-5 73270-43-6 73270-44-7 92740-48-2 130727-23-0
174298-44-3 174298-47-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of peptide contg. proline phosphonate derivs. as

inhibitors of serine proteases for therapeutics)
 IT 98-88-4P, Benzoyl chloride 350-71-0P 5679-61-8P 15516-41-3P
 65475-25-4P 152904-82-0P 174298-45-4P 174298-46-5P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (prepn. of peptide contg. proline phosphonate derivs. as
inhibitors of serine proteases for therapeutics)

L10 ANSWER 13 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1995:499553 CAPLUS

DN 123:50579

TI Myosin heavy chain-degrading proteinase from spear squid muscle

AU Ebina, Hiizu; Nagashima, Yuji; Ishizaki, Shoichiro; Taguchi, Takeshi

CS Department of Food Science and Technology, Tokyo University of Fisheries,
 Tokyo, 108, Japan

SO Food Research International (1995), 28(1), 31-6

CODEN: FORIEU; ISSN: 0963-9969

PB Elsevier

DT Journal

LA English

AB A trypsin-like proteinase responsible for textural deterioration of thermally induced gel was purified to apparent homogeneity from spear squid Loligo bleekeri mantle muscle by chromatog. on Sephacryl S-400 and DEAE Sepharose. The enzyme gave a protein band with a mol. wt. of 42 kDa on SDS-PAGE. The proteinase readily hydrolyzed casein, synthetic peptide butyloxycarbonyl-valine-leucine-lysine-4-methylcoumaryl-7-amide (Boc-Val-Leu-Lys-MCA) and myosin heavy chain. The proteolytic activity was effectively **inhibited by serine protease inhibitors** such as soybean trypsin inhibitor and N.alpha.-p-tosyl-L-lysine-chloromethyl ketone, but was not affected by the other types of **protease inhibitors** (e.g., EDTA, EGTA, iodoacetic acid, mercuric chloride and N-tosyl-L-phenylalanine-chloromethyl ketone). The optimal temp. was 40.degree. for hydrolysis of both casein and Boc-Val-Leu-Lys-MCA. The optimal pH values were 6.8 and 7.9 for the caseinolytic and peptide-hydrolyzing activity, resp. The proteolytic activity was increased 1.3-fold by addn. of 0.25M NaCl, but not by the addn. of Ca²⁺. Myosin heavy chain was shown to be cleaved into smaller fragments by incubation with the proteinase on SDS-PAGE. These results revealed that the enzyme was involved in degrdn. of myosin heavy chain from the squid mantle meat.

L10 ANSWER 14 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1995:440581 CAPLUS

DN 122:259635

TI NS3-4A of hepatitis C virus is a chymotrypsin-like protease

AU Hahm, Bumsuk; Han, Dae Sung; Back, Sung Hoon; Song, Ok-Kyu; Cho, Myung-Jae; Kim, Chul-Joong; Shimotohno, Kunitada; Jang, Sung Key

CS Department Life Science, Pohang University Science Technology, Pohang,
 790-784, Japan

SO Journal of Virology (1995), 69(4), 2534-9

CODEN: JOVIAM; ISSN: 0022-538X

PB American Society for Microbiology

DT Journal

LA English

AB The polyprotein encoded by a single open reading frame of hepatitis C virus (HCV) is processed by host- and virus-encoded **proteases**. The viral **protease** NS3 is responsible for the cleavage of at least four sites (NS3/4A, NS4A/4B, NS4B/5A, and NS5A/5B junctions) in the nonstructural protein region. To characterize the **protease** function of NS3 and NS4 on various target sites, efficient cis- and trans-cleavage assay systems were developed by using in vitro transcription and translation. Deletion of the C-terminal two-thirds from

NS3 in an NS3-NS4A-4B polypeptide (NS3.DELTA.C-4A-4B) hampered cleavage of the NS3/4A junction but not that of the NS4A/4B junction. As a consequence, expression of NS3.DELTA.C-4A-4B contg. an internal deletion of NS3 results in an NS3.DELTA.C-4A fusion protein. NS3.DELTA.C-4A shows very efficient and specific trans-cleavage activity at NS4A/4B, NS4B/5A, and NS5A/5B junctions. In addn., the biochem. properties of HCV NS3.DELTA.C-4A were further elucidated by adding known **protease inhibitors** in trans-cleavage reactions. The HCV **protease** NS3-4A is **inhibited** by chymotrypsin-specific **inhibitors** N-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK), chymostatin, and Pefabloc SC but not by trypsin-like **protease inhibitors** antipain, leupeptin, and N-.alpha.-p-tosyl-L-**lysine** chloromethyl ketone (TLCK) or by the **protease inhibitors** E-64, bestatin, pepstatin, and phosphoramidon. This finding strongly suggests that HCV **protease** NS3-4A is a chymotrypsin-like **serine** **protease**.

L10 ANSWER 15 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1995:12109 CAPLUS

DN 122:26398

TI Characterization of three neutral proteases of *Spirometra mansoni* plerocercoid

AU Kong, Y.; Chung, Y. -B.; Cho, S. -Y.; Choi, S. -H.; Kang, S. -Y.

CS Coll. Med., Chung-Ang Univ., Seoul, 156-756, S. Korea

SO Parasitology (1994), 108(3), 359-68

CODEN: PARAAE; ISSN: 0031-1820

DT Journal

LA English

AB In the pathogenesis of sparganosis, **proteases** have been considered to play important roles in tissue migration and parasite feeding. Several bands of proteolysis were obsd. when crude exts. of *Spirometra mansoni* plerocercoid (sparganum) were examd. using gelatin substrate gel at neutral pH, of which two **proteases** of 198 and 104 kDa were purified by two chromatog. steps, and a 36 kDa **protease** was purified by gelatin-affinity and DEAE-anion exchange chromatog. All the purified **proteases** exhibited optimal activity at pH 7.5 and 0.1 M Tris-HCl. Proteolytic activities at 198 and 104 kDa were **inhibited** specifically by **serine** **protease inhibitors**, and 4-(amidinophenyl)methansulfonyl fluoride (APMSF, 0.5 mM) and N-.alpha.-p-tosyl-L-**lysine** chloromethyl ketone (TLCK, 1 mM), which strongly suggested that these two **proteases** were trypsin-like **proteases**. The activity of the 36 kDa **protease** was **inhibited** by N-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK, 1 mM), and chymostatin (0.1 mM), and was potentiated in 10 mM Ca²⁺ which showed that the **protease** had a chymotrypsin-like property. All the **proteases** were Schiff (PAS) pos. **Proteases** of 198 and 104 kDa degraded collagen completely within 24 h. The 36 kDa enzyme cleaved human recombinant interferon-.gamma. (rIFN.gamma.) and bovine myelin basic protein. In addn., all the purified proteins elicited strong antibody responses in the infected patients.

(FILE 'HOME' ENTERED AT 11:06:39 ON 20 JUN 2003)

FILE 'CAPLUS' ENTERED AT 11:06:44 ON 20 JUN 2003

L1 38789 S PROTEAS? (L) INHIBIT?
L2 116 S L1 (L) (LYSINE(L) PHENYLALANINE)
L3 66 S L2 AND (LYSINE(10A) PHENYLALANINE)
L4 58 S L3 AND PY<1999
L5 1 S L4 AND P/DT
L6 57 S L4 NOT L5
L7 20 S L6 AND (SERINE(10A) PROTEASE)

=> l1 and (serine(10a)protease)

L1 IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system.

For a list of commands available to you in the current file, enter

"HELP COMMANDS" at an arrow prompt (=>).

=> s l1 and (serine(10a)protease)

89713 SERINE
75675 PROTEASE
9624 SERINE(10A) PROTEASE
L8 5755 L1 AND (SERINE(10A) PROTEASE)

=> s l8 and (lysine(l)phenylalanine)

90278 LYSINE
67940 PHENYLALANINE
9090 LYSINE(L) PHENYLALANINE
L9 49 L8 AND (LYSINE(L) PHENYLALANINE)

=> s l9 not l7

L10 29 L9 NOT L7

=> d bib hit 16-29

L10 ANSWER 16 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1993:226008 CAPLUS

DN 118:226008

TI The detection and isolation of protease activity associated with purified preparations of human chorionic gonadotropin

AU Daja, Mirella M.; Hiyama, Jun; Scott, G. Kenneth; Renwick, Alistair G. C.

CS Dep. Biochem., Univ. Auckland, Auckland, N. Z.

SO Endocrinology (1993), 132(4), 1766-73

CODEN: ENDOAO; ISSN: 0013-7227

DT Journal

LA English

AB The highly purified human chorionic gonadotropin (hCG) CR series is widely used as a ref. material in immunol. and biol. assays. However, these hormone preps., specifically hCG (CR127), exhibit Arg-specific peptidase activity with synthetic peptide substrates. The putative **serine protease**-like activity assocd. with hCG (CR127) was almost completely **inhibited** by diisopropylfluorophosphate, soybean trypsin **inhibitor**, N-tosyl-L-**phenylalanine** chloromethyl ketone and to a lesser extent by N-.alpha.-p-tosyl-L-**lysine** chloromethyl ketone and was isolated after hydrophobic interaction and affinity chromatog. with soybean trypsin **inhibitor**, which indicated the presence of exogenous **protease** contaminants rather than intrinsic peptidase activity. [3H]-DFP labeling and SDS-PAGE of the isolated contaminants revealed 2 possible serine **proteases** of apparent mol. wts. 60,000 and 20,000. The presence of these contaminants had no apparent effect on the receptor binding capability of hCG; however, the in vitro biol. activity of hCG detd. by maximal cAMP prodn. was decreased after hydrophobic interaction chromatog.

purifn. of the hormone. These observations suggest that the **serine protease**-like contaminants enhance cAMP prodn., thereby introducing a significant source of error in biol. assays that use hCG (CR127). Further purifn. of hCG by hydrophobic interaction and affinity chromatog. is recommended before its use in bioassays or research.

ST chorionic gonadotropin prepn **serin protease** contamination

IT Receptors

RL: SPN (Synthetic preparation); PREP (Preparation)
(gonadotropin, chorionic gonadotropin binding by, **serine protease** contamination of purified preps. in relation to)

IT Gonadotropins

RL: SPN (Synthetic preparation); PREP (Preparation)
(receptors, chorionic gonadotropin binding by, **serine protease** contamination of purified preps. in relation to)

IT 37259-58-8, **Serine protease**

RL: BIOL (Biological study)
(chorionic gonadotropin from human purified preps. contamination by, detection and isolation of)

IT 60-92-4, CAMP

RL: FORM (Formation, nonpreparative)
(formation of, chorionic gonadotropin stimulation of, **serine protease** contamination of purified preps. enhancement of)

IT 9002-61-3, Chorionic gonadotropin

RL: BIOL (Biological study)
(**serine protease** contamination of purified preps. of human, detection and isolation of)

L10 ANSWER 17 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1991:202438 CAPLUS

DN 114:202438

TI Site-directed mutagenesis of alanine-382 of human antithrombin III

AU Austin, Richard C.; Rachubinski, Richard A.; Blajchman, Morris A.

CS Canad. Red Cross Blood Transfus. Serv., Hamilton, ON, L3N 3Z5, Can.

SO FEBS Letters (1991), 280(2), 254-8

CODEN: FEBLAL; ISSN: 0014-5793

DT Journal

LA English

AB Antithrombin III Hamilton is a structural variant of antithrombin III (AT-III) with normal heparin affinity but impaired **serine**

protease inhibitory activity. The mol. defect of AT-III-Hamilton is a substitution of threonine for alanine at amino acid residue 382. Recently it has been shown that both plasma-derived and cell-free-derived AT-III-Hamilton polypeptides act as substrates rather than **inhibitors** of thrombin and factor Xa. In the present study, the cell-free expression phagemid vector pGEM-3Zf(+)-AT-III1-432 was mutated at amino acid residue 382 of AT-III to generate 7 cell-free-derived variants. All these cell-free-derived AT-III variants were able to bind heparin as effectively as cell-free-derived normal AT-III. In terms of α -thrombin **inhibitory** activity each variant reacted differently. Variants could be grouped into 3 categories with respect to thrombin-AT-III complex formation: (1) near normal activity (glycine, isoleucine, leucine, valine); (2) low activity (threonine, glutamine); (3) no detectable activity (**lysine**). These data suggest that mutations at position 382 of AT-III may have a variable effect on **protease inhibitory** activity, depending on either the stability of the P12-P9 region of the exposed loop of AT-III, or the inability of the amino acid residue at position 382 to interact with a conserved hydrophobic pocket consisting of **phenylalanine** (at positions 77, 221 and 422) and isoleucine (position 412) residues.

L10 ANSWER 18 OF 29 CAPLUS COPYRIGHT 2003 ACS
 AN 1991:141238 CAPLUS
 DN 114:141238
 TI Influence of **protease** on **inhibitory** and stimulatory effects of interleukin 1.beta. on .beta.-cell function
 AU Welsh, Nils; Bendtzen, Klaus; Sandler, Stellan
 CS Dep. Med. Cell Biol., Uppsala Univ., Uppsala, S-751 23, Swed.
 SO Diabetes (1991), 40(2), 290-4
 CODEN: DIAEAZ; ISSN: 0012-1797
 DT Journal
 LA English
 TI Influence of **protease** on **inhibitory** and stimulatory effects of interleukin 1.beta. on .beta.-cell function
 AB To elucidate the putative role of **proteases** in the action of interleukin 1.beta. (IL-1.beta.) on pancreatic .beta.-cells, the authors studied the effects on islet function of different **protease inhibitors** when added together with recombinant IL-1.beta. to isolated rat pancreatic islets. The trypsin **inhibitor** n.alpha.-p-tosyl-L-lysine chloromethyl ketone (TLCK) counteracted the acute stimulatory effects of IL-1.beta. on islet glucose oxidn., insulin release, and biosynthesis. TLCK also partially or completely counteracted the long-term **inhibitory** effects of IL-1.beta. on islet glucose oxidn., insulin biosynthesis, content, and release. This **protease inhibitor** also counteracted IL-1.beta.-induced .beta.-cell cytotoxicity as assessed by DNA content measurements. Of the other group-specific **protease inhibitors** investigated, only n-tosyl-L-phenylalanine chloromethyl ketone, n.alpha.-p-tosyl-L-arginine Me ester, and chloromercuriphenylsulfonic acid were found to partially protect against IL-1.beta. action. It is concluded that **protease** activation, putatively a **serine protease**, may be an early and perhaps primary event in the action of IL-1.beta. on .beta.-cells.
 IT 402-71-1 901-47-3 2364-87-6, N.alpha.-p-Tosyl-L-lysine chloromethyl ketone
 RL: BIOL (Biological study)
 (interleukin 1.beta. effect on pancreatic .beta. cells
 inhibition by, **protease** in relation to)
 IT 37259-58-8, **Serine protease**
 RL: BIOL (Biological study)
 (interleukin 1.beta. effect on pancreatic .beta.-cells in relation to)

 L10 ANSWER 19 OF 29 CAPLUS COPYRIGHT 2003 ACS
 AN 1990:478910 CAPLUS
 DN 113:78910
 TI Synthesis of new phosphonate **inhibitors** of serine **proteases**
 AU Fastrez, Jacques; Jespers, Laurent; Lison, Dominique; Renard, Michel; Sonveaux, Etienne
 CS Louvain-la-Neuve, B-1348, Belg.
 SO Tetrahedron Letters (1989), 30(49), 6861-4
 CODEN: TELEAY; ISSN: 0040-4039
 DT Journal
 LA English
 OS CASREACT 113:78910
 TI Synthesis of new phosphonate **inhibitors** of serine **proteases**
 AB Phosphonate inhibitors AcNHCHRP(O)(OR1)OC6H4Cl-3 [I, R = CH2Ph, (CH2)4NH2; R1 = Et, 3-ClC6H4] were prep'd. as analogs of **phenylalanine** and **lysine** esters. The inhibitory powers of I were tested in vitro on chymotrypsin, trypsin, and urokinase.
 ST acetylphenylalanine phosphonate analog chymotrypsin **inhibitor**; trypsin **inhibitor** acetyllysine phosphonate analog; urokinase **inhibitor** acetyllysine phosphonate analog; **serine**

protease inhibitor acetylaminophosphonate prepn
 IT 37259-58-8, **Serine protease**
 RL: PROC (Process)
 (inhibition of, with acetylphenylalanine and acetyllysine phosphonate analogs)

L10 ANSWER 20 OF 29 CAPLUS COPYRIGHT 2003 ACS
 AN 1989:453055 CAPLUS
 DN 111:53055
 TI Novel **inhibitors** of human leukocyte elastase and cathepsin G. Sequence variants of squash seed **protease inhibitor** with altered **protease** selectivity
 AU McWherter, Charles A.; Walkenhorst, William F.; Campbell, Edward J.; Glover, George I.
 CS Dep. Biol. Sci., Monsanto Co., St. Louis, MO, 63198, USA
 SO Biochemistry (1989), 28(14), 5708-14
 CODEN: BICHAW; ISSN: 0006-2960
 DT Journal
 LA English
 TI Novel **inhibitors** of human leukocyte elastase and cathepsin G. Sequence variants of squash seed **protease inhibitor** with altered **protease** selectivity
 AB Novel peptide inhibitors of human leukocyte elastase (HLE) and cathepsin G (CG) were prepd. by solid-phase peptide synthesis of P1 amino acid sequence variants of Curcubita maxima trypsin inhibitor III (CMTI-III), a 29-residue peptide found in squash seeds. A systematic study of P1 variants indicated that P1 arginine, **lysine**, leucine (Leu), alanine (Ala), **phenylalanine** (Phe), and methionine (Met) inhibited trypsin; P1 valine (Val), isoleucine (Ile), glycine (Gly), Leu, Ala, Phe, and Met inhibited HLE; P1 Leu, Ala, Phe, and Met inhibited CG and chymotrypsin. Variants with P1 Val, Ile, or Gly were selective inhibitors of HLE, whereas inhibition of trypsin required P1 amino acids with an unbranched .beta.-C atom. Studies of Val-5-CMTI-III (P1 Val) inhibition of HLE demonstrated a 1:1 binding stoichiometry with an apparent K_i of 8.7 nM. The inhibition of HLE by Gly-5-CMTI-III indicated a significant role for reactive-site structural moieties other than the P1 side-chain. Val-5-CMTI-III inhibited both HLE and human polymorphonuclear leukocyte (PMN) proteolysis of surface-bound 125I-labeled fibronectin. Val-5-CMTI-III was more effective at preventing turnover of a peptide p-nitroanilide substrate than halting the dissoln. of 125I-labeled fibronectin. It was about as effective as human serum .alpha.1-proteinase inhibitor in preventing PMN degradn. of the connective tissue substrate. In addn. to providing interesting candidates for controlling inflammatory cell proteolytic injury, the CMTI-based inhibitors are ideal for studying mol. recognition because of their small size, their ease of prepn., and the availability of sensitive and quant. assays for intermol. interactions.
 ST **protease inhibitor** squash peptide analog prepn; trypsin **inhibitor** squash peptide analog prepn; elastase **inhibition** squash trypsin **inhibitor** analog; cathepsin G **inhibition** trypsin **inhibitor** analog; inflammation proteolytic injury **inhibition** peptide squash
 IT 9002-07-7, Trypsin 9004-07-3, Chymotrypsin 37259-58-8, **Serine protease**
 RL: PROC (Process)
 (inhibition of, by analogs of trypsin **inhibitor** III of squash seeds)

L10 ANSWER 21 OF 29 CAPLUS COPYRIGHT 2003 ACS
 AN 1989:227593 CAPLUS
 DN 110:227593
 TI Kinetics and specificity of serine proteases in peptide synthesis catalyzed in organic solvents

AU Gaertner, Hubert; Puigserver, Antoine
 CS Cent. Biochem. Biol. Mol., Marseille, F-13402, Fr.
 SO European Journal of Biochemistry (1989), 181(1), 207-13
 CODEN: EJBCAI; ISSN: 0014-2956
 DT Journal
 LA English
 AB Initial rates of peptide-bond synthesis catalyzed by poly(ethylene glycol)-modified chymotrypsin in benzene were detd. using HPLC. Enzymic synthesis of N-benzoyl-L-tyrosyl-L-**phenylalanine** amide from N-benzoyl-L-tyrosine Et ester and L-**phenylalanine** amide was found to obey Michaelis-Menten kinetics and to be consistent with a ping-pong mechanism modified by a hydrolytic branch. The catalytic activity of modified chymotrypsin was dependent on both concn. and type of org. solvent, the highest synthesis rate being obtained in toluene. Since the chymotrypsin specificity in the org. phase was actually altered, the enzyme's apparent kinetic parameters were detd. for differential substrates and compared to those obtained with other serine **proteases** in benzene. Both N-benzoyl-L-tyrosine Et ester and N-.alpha.-benzoyl-L-**lysine** Me ester were comparable acyl donors in benzene and the (kcat/Km)app value of modified chymotrypsin was only 10-fold smaller than that obtained with poly(ethylene glycol)-modified trypsin in the synthesis of N-.alpha.-benzoyl-L-lysyl-L-**phenylalanine** amide. The change in chymotrypsin specificity was also confirmed through the binding of trypsin **inhibitors** in benzene. The overall results suggest that hydrophobic bonding between the enzyme and its substrate should not be taken into account during catalysis in the org. phase. In general, if hydrophobic interactions are involved in the binding of substrates to the active site in aq. media, the replacement of water by hydrophobic solvent will induce some change in enzyme specificity. Moreover, secondary residues of enzyme-binding sites may also exert a significant influence on specificity since, as obsd. in this study, chymotrypsin exhibited high affinity for cationic substrates and cationic **inhibitors** as well in apolar solvents.

ST chymotrypsin kinetics specificity org solvent; **serine protease** kinetics specificity org solvent

L10 ANSWER 22 OF 29 CAPLUS COPYRIGHT 2003 ACS
 AN 1988:220161 CAPLUS
 DN 108:220161
 TI The effect of serine esterase inhibitors on ionophore-induced histamine release from human pulmonary mast cells
 AU Hultsch, T.; Ennis, M.; Heidtmann, H. H.
 CS Inst. Theor. Surg., Univ. Marburg, Marburg, D-3550, Fed. Rep. Ger.
 SO Agents and Actions (1988), 24(3-4), 198-200
 CODEN: AGACBH; ISSN: 0065-4299
 DT Journal
 LA English
 AB The serine **proteases** tryptase and chymase are present in human pulmonary mast cells. About 10-100-fold more tryptase than chymase is found in these cells. A dose-dependent **inhibition** of A23187-induced histamine release from dispersed human lung mast cells was obsd. after pretreatment with the **serine protease inhibitor** diisopropylfluorophosphate (DFP) or the chymotrypsin-like enzyme **inhibitor** N-tosyl-L-**phenylalanine** chloromethylketone (TPCK) but not with the trypsin-like enzyme **inhibitor** N-tosyl-L-**lysine** chloromethylketone (TLCK). Thus, a chymase is probably an important factor in the late phase of human lung mast cell activation.

L10 ANSWER 23 OF 29 CAPLUS COPYRIGHT 2003 ACS
 AN 1987:418274 CAPLUS
 DN 107:18274
 TI .beta.-Adrenergic receptor modification with **serine**

protease inhibitors

- AU Voeikov, V. L.; Udovichenko, I. P.; Kiselev, O. G.; Prokhorova, I. A.
CS Biol. Fac., M. V. Lomonosov Moscow State Univ., Moscow, USSR
SO Biologicheskii Membrany (1987), 4(4), 438-42
CODEN: BIMEE9; ISSN: 0233-4755
DT Journal
LA Russian
TI .beta.-Adrenergic receptor modification with **serine**
protease inhibitors
AB The proteinase inhibitors diisopropylfluorophosphate (DFP),
phenylmethanesulfonylfluoride (PMSF), N-.alpha.-p-tosyl-L-**lysine**
chloromethyl ketone (TLCK), or N-p-tosyl-L-**phenylalanine**
chloromethyl ketone (TPCK) decreased dihydroalprenolol binding by highly
purified bovine cerebellum .beta.-adrenergic receptors reconstituted into
phospholipid vesicles. TLCK, PMSF, and DFP, but not TPCK, also decreased
ligand binding by .beta.-receptors from bovine cerebellum membrane and
TLCK and TPCK decreased that by frog erythrocyte membrane, but none of the
proteinase inhibitors affected ligand binding by intact frog erythrocytes.
[3H]DFP covalently labeled reconstituted .beta.-receptors. TLCK,
isoproterenol, and, to a lesser extent, propranolol abolished this
labeling. A comparison of the primary structure of the mammalian
.beta.-receptor and chymotrypsin revealed 3 short regions of homol., 2 of
which are adjacent to His and Asp residues of the active center of
chymotrypsin and 1 includes the active Ser195 which coincides with Ser408
of the receptor. Apparently, .beta.-adrenergic receptors possess a site
similar to the active site of serine proteinases. This site is likely to
be localized on the cytoplasmic surface of the cell membrane.
IT Receptors
RL: PROC (Process)
 (.beta.-adrenergic, **serine protease**
 inhibitors modification of)
IT 7683-59-2
RL: BIOL (Biological study)
 (.beta.-adrenergic receptor binding of **protease**
 inhibitor abolition by)

L10 ANSWER 24 OF 29 CAPLUS COPYRIGHT 2003 ACS
AN 1983:486507 CAPLUS
DN 99:86507
TI Analysis of proteases involved in phagocytic activity of macrophages
through the use of various amino acid esters
AU Nihira, Shinichi; Koyama, Jiro
CS Fac. Pharm. Sci., Hokkaido Univ., Sapporo, 060, Japan
SO Journal of Biochemistry (Tokyo, Japan) (1983), 94(2), 565-73
CODEN: JOBIAO; ISSN: 0021-924X
DT Journal
LA English
AB The **inhibitory** effects of various amino acid esters on the
phagocytic activity of guinea pig peritoneal macrophages were studied with
antibody-coated 51Cr-labeled sheep erythrocytes (51Cr-EAb) as well as
125I-labeled-.alpha.-amylase complexed with homologous IgG2 antibody
(Ag-Ab complex). The intracellular uptake of 51Cr-EAb was markedly
inhibited by the chymotrypsin substrates, N-acetyl-L-
phenylalanine Et ester (Ac-Phe-OEt), N-acetyl-L-tryptophan Et
ester (Ac-Trp-OEt), and N-benzoyl-L-tyrosine Et ester (Bz-Tyr-OEt), but
not by N-acetyl-L-tyrosine Et ester (Ac-Tyr-OEt) and not by the trypsin
substrates, N-.alpha.-acetyl-L-arginine Me ester, N-.alpha.-benzoyl-L-
arginine Et ester (Bz-Arg-OEt), or N-.alpha.-acetyl-L-**lysine** Me
ester. When phagocytosis of the Ag-Ab complex was assayed by measuring
the amt. of digested products released from macrophage cells, Ac-Tyr-OEt
also **inhibited** it as markedly as Ac-Phe-OEt, Ac-Trp-OEt, and
Bz-Tyr-OEt did, whereas Bz-Arg-OEt again did not show any effect. The
results of anal. of the intracellular fate of the Ag-Ab complex taken up

by macrophages, through the use of anal. d. gradient fractionation of the homogenized cells, suggest that Ac-Phe-OEt **inhibits** the ingestive process since the distribution of Ag-Ab complex showed a single peak, closely accompanying the plasma membrane. Ac-Tyr-OEt, on the other hand, caused a marked accumulation of Ag-Ab complex in the lysosome fraction, reflecting the **inhibition** of intralysosomal digestion of the complex. These results may classify the chymotrypsin substrates tested into 3 groups: 1) Ac-Phe-OEt and Ac-Trp-OEt **inhibiting** the ingestive process in phagocytosis, probably more strongly than the digestive process; 2) Bz-Tyr-OEt **inhibiting** both the ingestive and digestive processes and 3), Ac-Tyr-OEt **inhibiting** the digestive process alone. In addn., this classification of the chymotrypsin substrates may support the hypothesis that a certain chymotrypsin-like **serine protease** with a high substrate-specificity is involved in the ingestive process of immune complexes in macrophages.

IT 840-97-1 971-21-1 2361-96-8 2382-80-1 3483-82-7 6072-02-2
6072-07-7

RL: BIOL (Biological study)

(macrophage phagocytosis **inhibition** by, chymotrypsin-like
protease in)

L10 ANSWER 25 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1983:87001 CAPLUS

DN 98:87001

TI Effect of an extract of Nereis virens on mammalian spermatozoa

AU Gordon, Mildred; Morris, Eugene G.; Stark, Freddy; Williams, William L.;
Young, Ron J.

CS Sch. Biomed. Educ., City Coll., New York, NY, 10031, USA

SO Gamete Research (1982), 6(4), 353-63

CODEN: GAMRDC; ISSN: 0148-7280

DT Journal

LA English

AB Epididymal sperm of the mouse, rat, and guinea pig and ejaculated sperm of rabbits are cleaved at the head-tail junction by an ext. of N. virens. Electron microscopy shows that the ext. acts on the filaments connecting the capitulum of the tail with the basal plate lining the nuclear envelope. Following detachment, the basal plate remains with the head. The ext. contains **proteases** as indicated by hydrolysis of tosyl arginine Me ester (TAME), BAEE, and Azocoll, a general **protease** substrate. The hydrolysis of TAME is **inhibited** by TLCK, a trypsin **inhibitor**, but TLCK does not prevent head-tail sepn. by the Nereis ext. Similarly, tosyl **phenylalanine** chloromethyl ketone (TPCK), a chymotrypsin **inhibitor**, and phosphoramidon and leucyltryptophan, both thermolysin and acrolysin **inhibitors**, either singly or in combination, do not prevent hydrolysis of Azocoll. Head-tail sepn. activity of the ext. was **inhibited** by dithiothreitol, which reduces disulfide bonds, and phenylmethyl sulfonyl fluoride, an **inhibitor** of serine **proteases**. Evidently, the ext. is a mixt. of **proteases**, one being a **serine protease** similar to trypsin. Digestion of the connecting filaments with pure **proteases**, trypsin and Staphylococcus aureus V8 **protease**, has yielded the following information on the proteins of the filaments. The accessibility of arginine and (or) **lysine** peptide bonds to enzyme action is highest in rat sperm filaments, whereas those in the filaments of mouse, rabbit, and guinea pig sperm are less accessible than those in the rat. Another possibility is that the total content of arginine and (or) **lysine** varies among the species. The most dramatic difference is the enzymic action on glutamyl peptide bonds of the filaments, the order being: mouse > rat > rabbit, with guinea pig sperm filaments completely resistant over the time course of the expt.

L10 ANSWER 26 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1980:38507 CAPLUS

DN 92:38507

TI **Serine protease inhibitors inhibit**

superoxide production by human polymorphonuclear leukocytes and monocytes stimulated by various surface active agents

AU Kitagawa, Seiichi; Takaku, Fumimaro; Sakamoto, Shinobu

CS Dep. Hematol., Jichi Med. Sch., Minamikawachi, 329-04, Japan

SO FEBS Letters (1979), 107(2), 331-4

CODEN: FEBLAL; ISSN: 0014-5793

DT Journal

LA English

TI **Serine protease inhibitors inhibit**

superoxide production by human polymorphonuclear leukocytes and monocytes stimulated by various surface active agents

AB Serine proteinases (I) of polymorphonuclear leukocyte (PMN) and monocyte cell membranes apparently are involved in superoxide release by these cells. I inhibitors (phenylmethylsulfonyl fluoride, L-1-tosylamido-2-phenylethyl chloromethyl ketone, and N-.alpha.-.pi.-tosyl-L-lysine chloromethyl ketone) and synthetic substrates (N-benzoyl-L-tyrosine Et ester and p-tosyl-L-arginine Me ester) inhibited superoxide prodn. by human PMNs and monocytes as induced by the surface active agents wheat germ agglutinin, N-formylmethionyl **phenylalanine**, phorbol myristate acetate, Ca ionophore A23187, and phospholipase C (the latter 2 compds. were active only on PMNs and not on monocytes). The action mechanism of the various superoxide inducers are different and this difference was reflected in the different degrees of inhibition of superoxide release by I inhibitors and substrates.

L10 ANSWER 27 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1979:470659 CAPLUS

DN 91:70659

TI Purification, characterization and localization of **serine protease** of Morris hepatoma 8999

AU Banno, Yoshiko; Morris, Harold P.; Katunuma, Nobuhiko

CS Sch. Med., Tokushima Univ., Tokushima, Japan

SO European Journal of Biochemistry (1979), 97(1), 11-21

CODEN: EJBCAI; ISSN: 0014-2956

DT Journal

LA English

TI Purification, characterization and localization of **serine protease** of Morris hepatoma 8999

AB A **serine protease** of hepatoma 8999, isolated in the mitochondrial fraction, was purified and crystd. The purified enzyme was apparently homogeneous on ultracentrifugal anal. and polyacrylamide disc gel electrophoresis. The ratio of absorbance at 280 nm and 260 nm, A280/A260, was 1.90 and the absorption coeff., A2801%, was 10.5 cm⁻¹ estd. from dry. wt. measurements. The sedimentation coeff. was 2.23 S and the mol. wt. was 24,000. The enzyme contained twice as much **lysine**, arginine, and histidine as chymotrypsinogen, but had a very similar amino acid compn. to **serine protease** from skeletal muscle. The isoelec. point was pH 10.6. The substrate specificity of the enzyme was the same as that of chymotrypsin A. The Km and kcat values for N-acetyl-L-tyrosine Et ester, N-acetyl-L-**phenylalanine** Et ester, and N-acetyl-L-tryptophan Et ester were 0.35 mM and 10.69 s⁻¹, 0.38 mM and 10.7 s⁻¹, and 0.11 mM and 11.8 s⁻¹, resp. The activity was completely **inhibited** by phenylmethylsulfonyl fluoride and partially **inhibited** by tosylphenylalanine chloromethyl ketone. The enzyme was located in different granules from the intracellular particules (light and heavy mitochondrial fraction) by sucrose d. gradient centrifugation, and it was stained in mast cells of the hepatoma 8999 by the immunofluorescent technique. **Serine proteases** were present in different amts. in various organs of rat. The enzyme from hepatoma 8999

gave a single band that fused completely with those of the enzymes from skeletal muscle, heart, liver, and kidney, resp., on Ouchterlony double-diffusion anal. using antiserum to the cryst. enzyme of hepatoma 8999; the enzyme from small intestine did not react with the antiserum.

ST **serine protease** hepatoma; chymotrypsin protease hepatoma

L10 ANSWER 28 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1978:457216 CAPLUS

DN 89:57216

TI **Inhibition of bovidae oocyte meiosis by serine protease inhibitors**

AU Jagiello, Georgiana; Ducayen, Mercedes; Goonan, William; Downey, Susan
CS Cent. Reprod. Sci., Columbia Univ. Coll. Physicians Surg., New York, NY, USA

SO Proceedings of the Society for Experimental Biology and Medicine (1978), 157(4), 550-2

CODEN: PSEBAA; ISSN: 0037-9727

DT Journal

LA English

TI **Inhibition of bovidae oocyte meiosis by serine protease inhibitors**

AB In bovine oocytes in vitro, the approx. concns. required to inhibit maturation of 50% of the oocytes relative to controls were 0.1 mM for N-p-tosyl-L-lysine chloromethyl ketone, a trypsin inhibitor, phenylmethylsulfonyl fluoride, an inhibitor of esterase involved in the phosphorylation of serine residues, and di-Ph carbamyl chloride, a chymotrypsin inhibitor, 0.3 mM for N-p-tosyl-L-phenylalanine chloromethyl ketone, a chymotrypsin inhibitor; and 3.0 mM for N-tosyl arginine Me ester-HCl, a trypsin substrate analog. The natural **serine protease inhibitor** serum .alpha.u-antitrypsin (10 mg/mL) also prevented maturation in 94 oocytes. Serine **proteases** may be involved in bovine oocyte maturation.

ST **serine protease** egg meiosis; trypsin egg meiosis; chymotrypsin egg meiosis

L10 ANSWER 29 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 1974:92547 CAPLUS

DN 80:92547

TI Heterogeneity of Streptomyces griseus **protease**. Isolation and characterization of an alkaline **serine protease** from commercial Pronase-P derived from Streptomyces griseus K1

AU Bauer, Carl Axel; Lofqvist, Bo

CS Biochem. 1, Chem. Cent., Lund, Swed.

SO Acta Chemica Scandinavica (1947-1973) (1973), 27(9), 3147-66

CODEN: ACSAA4; ISSN: 0001-5393

DT Journal

LA English

TI Heterogeneity of Streptomyces griseus **protease**. Isolation and characterization of an alkaline **serine protease** from commercial Pronase-P derived from Streptomyces griseus K1

AB A proteolytic enzyme was isolated from Pronase-P by gel filtration on Sephadex G-75 superfine. The yield was almost optimal and the specific activity of the enzyme was const. throughout the isolation procedure and storage. Anal. polyacrylamide gel electrophoresis at pH 6.8 and 8.5 failed to reveal any impurities in the prepn. When the enzyme was concd. 5-10 fold, 2 minor contaminants were detected. They were estd. by staining to constitute < 2% and by enzymic activity < 1%. The binding of Ca²⁺ to the enzyme was found to be nonstoichiometric, and leading to a higher electrophoretic mobility with increasing Ca²⁺-content in the buffer. In Ca²⁺-free media the enzyme has an isoelec. point just > 7. The mol. wt. was estd. at 18,000. The most striking feature of the amino

acid anal. was that no **lysine** was detected. The enzyme was most stable in Ca²⁺-contg. buffers of neutral pH. In such buffers, the enzyme was also stable in the pH range 5-11, in this respect being similar to elastase. The pH optimum of the enzyme towards glutarylphenylalanine p-nitroanilide was between pH 10 and 11. The enzyme was **inhibited** completely by diisopropyl fluorophosphate, and partly by **inhibitors** normally considered to be site-specific for either chymotrypsin or elastase. The enzyme was highly active towards acetyl-L-tyrosine Et ester, (carbobenzoxy)tyrosine p-nitrophenyl ester, and glutaryl-L-**phenylalanine** p-nitroanilide. It was also active towards acetyl-alanyl-alanyl-alanine Me ester and Congo Red elastin as well as towards many other substrates. The activity towards casein at pH 7.5 and pH 10 was approx. identical. Amidase activity of the enzyme was low. The enzyme was classified as an alk. **serine protease** with broad substrate specificity, showing similarities with both chymotrypsin and elastase. The results are discussed in relation to earlier investigations on this and similar enzymes.

ST alk protease Streptomyces; Pronase **serine protease** component

=> d bib hit 1-15

L10 ANSWER 1 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 2001:839395 CAPLUS

DN 136:116732

TI Involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture

AU Mitsui, Chizu; Sakai, Kazuhisa; Ninomiya, Takafumi; Koike, Tatsuro

CS Molecular Neurobiology Laboratory, Graduate School of Science, Hokkaido University, Sapporo, 060-0810, Japan

SO Journal of Neuroscience Research (2001), 66(4), 601-611

CODEN: JNREDK; ISSN: 0360-4012

PB Wiley-Liss, Inc.

DT Journal

LA English

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture

AB Superior cervical ganglion (SCG) cells from neonatal rats underwent apoptosis upon treatment with colchicine, a microtubule-disrupting agent. Western blotting and activity measurements showed that caspase-3 was indeed activated, but its peptide **inhibitor** (Ac-DEVD-CHO) neither suppressed nuclear fragmentation nor rescued the neurons from cell death. Z-VAD-fmk, the general **inhibitor** of caspases, prevented nuclear fragmentation and delayed the cell death. Moreover, N-.alpha.-tosyl-L-**lysine** chloromethyl ketone (TLCK), but not N-.alpha.-tosyl-L-**phenylalanine** chloromethyl ketone (TPCK), prevented nuclear fragmentation and provided neuronal protection as well. The combination of both z-VAD-fmk and TLCK provided a long-term neuronal protection (>4 days); whereas neither one alone could do so, suggesting that there are both caspase-dependent and -independent pathways. TLCK-sensitive **serine protease** is also likely to act upstream of caspase-3 in a caspase-dependent pathway. Electron microscopic observations demonstrated that z-VAD-fmk suppressed nuclear fragmentation and improved mitochondrial swelling, but failed to prevent vesicular formation, which resulted in a slowly-occurring necrosis. More importantly, TLCK effectively blocked this abundant vesicular formation along with suppressing chromatin condensation. Thus, the combination of both conferred a nearly normal morphol., which is consistent with the results of cell survival expts. These findings clearly indicate that TLCK-sensitive **serine protease** plays multiple roles in

caspase-dependent and -independent pathways of colchicine-induced cell death, and suggest a novel mechanism underlying a necrotic pathway involving ER swelling and vesicular formation.

- ST **serine protease** sympathetic neuron apoptosis necrosis
caspase
- IT Nerve, disease
(death; involvement of TLCK-sensitive **serine protease**
in colchicine-induced cell death of sympathetic neurons in culture)
- IT Nervous system
(disease; involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)
- IT Apoptosis
Mitochondria
Necrosis
Newborn
(involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)
- IT Cell death
(neuron; involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)
- IT Ganglion
(superior cervical sympathetic; involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)
- IT 37259-58-8, **Serine protease**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TLCK-sensitive; involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)
- IT 402-71-1, N-.alpha.-Tosyl-L-phenylalanine chloromethyl ketone 2364-87-6
169592-56-7, Caspase-3 220644-02-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)
- IT 64-86-8, Colchicine
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
(Uses)
(involvement of TLCK-sensitive **serine protease** in colchicine-induced cell death of sympathetic neurons in culture)

L10 ANSWER 2 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 2000:478833 CAPLUS

DN 134:14577

TI Identification and characterisation of the excreted/secreted serine proteases of larvae of the Old World screwworm fly, *Chrysomya bezziana*

AU Muharsini, Sri; Sukarsih; Riding, George; Partoutomo, Sutijono; Hamilton, Susan; Willadsen, Peter; Wijffels, Gene

CS CSIRO Tropical Agriculture, Molecular Animal Genetics Centre, Level 3, Gehrmann Laboratories, University of Queensland, Queensland, 4072, Australia

SO International Journal for Parasitology (2000), 30(6), 705-714
CODEN: IJPYBT; ISSN: 0020-7519

PB Elsevier Science Ltd.

DT Journal

LA English

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB **Serine proteases** are the major proteolytic activity excreted or secreted from *Chrysomya bezziana* larvae as demonstrated by gelatin gel analyses and the use of specific substrates, benzoyl-Arg-p-nitroanilide and succinyl-Ala-Ala-Pro-Phe-p-nitroanilide. **Serine proteases**

were identified through their **inhibition** by 4-(2-aminoethyl)-benzene sulfonyl fluoride and classified as trypsin- and chymotrypsin-like on the basis of **inhibition** by tosyl-L-lysine chloromethyl ketone and tosyl-L-phenylalanine chloromethyl ketone, resp. Like most insect serine **proteases**, the C. bezziana enzymes were active over broad pH range from mildly acidic to alk. The excreted or secreted serine **proteases** were purified by affinity chromatog. using soybean trypsin **inhibitor**. A different subset of the serine **proteases** was isolated by salt elution from washed larval peritrophic matrixes. Aminoterminal sequencing identified both trypsin and chymotrypsin-like sequences in the excreted or secreted pool with the latter being the dominant **protease**, whereas trypsin was the dominant species in the peritrophic matrix eluant. These results suggest that trypsin was possibly preferably adsorbed by the peritrophic matrix and may act as a final proteolytic processing stage as partially digested and ingested polypeptides pass through the peritrophic matrix. Immunoblot anal. on dissected gut tissues indicated that the anterior and posterior midguts were the main source of the serine **proteases**, although a novel species of 32 kDa was predominantly assocd. with the peritrophic matrix. **Proteases** are a target for a partially protective immune response and understanding the complexity of the secreted and digestive **proteases** is a necessary part of understanding the mechanism of the host's immunol. defense against the parasite.

ST screwworm fly **serine protease** chymotrypsin trypsin

IT 37259-58-8P, **Serine protease**

RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)

(trypsin- and chymotrypsin-like; identification and characterization of excreted/secreted **serine** proteases of larvae of Old World screwworm fly, Chrysomya bezziana)

L10 ANSWER 3 OF 29 CAPLUS COPYRIGHT 2003 ACS

AN 2000:201999 CAPLUS

DN 132:306250

TI A role for serine proteases in mediating phorbol ester-induced differentiation of HL-60 cells

AU Bestilny, Leslie J.; Riabowol, Karl T.

CS Departments of Biochemistry & Molecular Biology and Oncology, The University of Calgary Health Sciences Centre, Calgary, AB, T2N 4N1, Can.

SO Experimental Cell Research (2000), 256(1), 264-271

CODEN: ECREAL; ISSN: 0014-4827

PB Academic Press

DT Journal

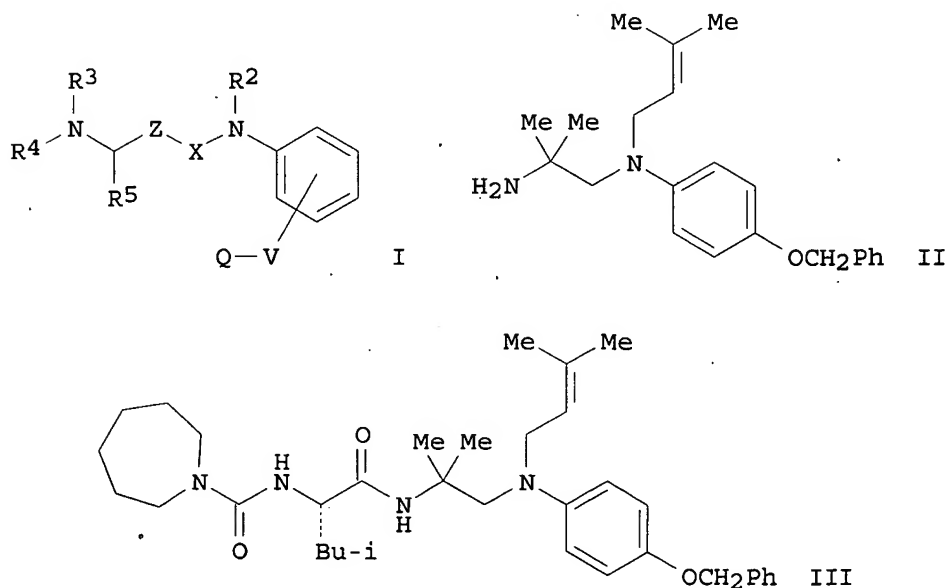
LA English

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Treatment of human HL-60 promyelocytic leukemia cells with the phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA), results in increases in proteolytic activity and maturation toward the monocytic lineage. To investigate the potential roles that different classes of **proteases** play in the monocytic differentiation of HL-60 cells, cells were treated with TPA in the presence of various **serine** and cysteine **protease inhibitors**. The **serine protease inhibitors**, 4-(2-aminoethyl)-benzenesulfonyl fluoride (AEBSF), N-.alpha.-tosyl-**phenylalanine** chloromethyl ketone (TPCK), and N-.alpha.-tosyl-**lysine** chloromethyl ketone (TLCK), repressed a no. of phenotypic markers of monocytic differentiation including surface expression of CD11b integrin, cell aggregate formation, cell cycle exit, and cell death. CD11b was not detected at the cell surface by FACS anal. up to 24 h after induction of differentiation; however, both CD11b mRNA and protein were present. Down-regulation of

AN 1999:126886 CAPLUS
 DN 130:196584
 TI Preparation of aniline derivatives as calcium channel blockers
 IN Hu, Lain-Yen; Rafferty, Michael Francis; Ryder, Todd Robert
 PA Warner-Lambert Company, USA
 SO PCT Int. Appl., 137 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9907689	A1	19990218	WO 1998-US15907	19980729 <--
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9887627	A1	19990301	AU 1998-87627	19980729 <--
	ZA 9807144	A	19990510	ZA 1998-7144	19980807 <--
	US 6251918	B1	20010626	US 1999-402196	19990929
	US 2001023249	A1	20010920	US 2001-769798	20010125
	US 6495715	B2	20021217		
	US 2003060632	A1	20030327	US 2002-252854	20020923
PRAI	US 1997-55251P	P	19970811		
	US 1998-82358P	P	19980420		
	WO 1998-US15907	W	19980729		
	US 1999-402196	A3	19990929		
	US 2001-769798	A3	20010125		
OS	MARPAT 130:196584				
GI					



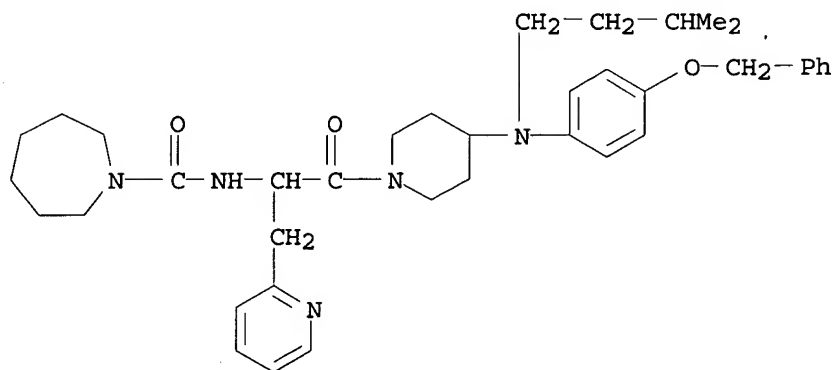
AB The invention provides compds. that block calcium channels. In

particular, the invention claims compds. I [Z = CH₂ or CO; X = cycloalkylene, (un)substituted heterocycloalkylene, imino or iminoalkylene, certain piperidinediyl or pyrrolidinediyl radicals or their alkylene derivs.; Q = H, (un)substituted aryl, heteroaryl, cycloalkyl, alkyl, heterocycloalkyl; V = O(CH₂)_n or (CH₂)_nO, O, (CH₂)_n, CH:CH, NH(CH₂)_n or (CH₂)_nNH or derivs.; R₂ = H, alkenyl, cycloalkenyl, (un)substituted Ph, alkyl, cycloalkyl, or Ph; R₃ = H, alkyl, alkenyl; R₄ = H, cyclo-(CH₂)_mNCO, alkyl, alkenyl, (un)substituted Ph, heteroaryl, or cycloalkyl; or NR₃R₄ = 5- to 7-membered ring with an optional addnl. heteroatom; R₅ = alkyl, (un)substituted Ph or heteroaryl; m = 1-3; n = 0-3] and their pharmaceutically acceptable salts, esters, amides, and prodrugs. The invention also provides methods of using the compds. to treat stroke, cerebral ischemia, head trauma, or epilepsy, and to pharmaceutical compns. that contain the compds. Over 50 synthetic examples are given, and these plus a large no. of addnl. invention compds. are specifically claimed. For instance, N-BOC-.alpha.-aminoisobutyric acid underwent amidation with 4-benzyloxyaniline, followed by redn. of the amide with diborane, N-alkenylation with 4-bromo-2-methyl-2-butene, and acidic deprotection to remove BOC, to give intermediate II. In a sep. prepn., H-Leu-OCH₂Ph was treated with triphosgene and hexamethylenamine, then deprotected, to give Hac-Leu-OH (III; Hac = hexamethylenaminocarbonyl). Coupling of II with III using HBTU and DIPEA in DMF gave title compd. IV. The latter blocked calcium flux through N-type Ca²⁺ channels in IMR-32 neuronal tumor cells in vitro, with IC₅₀ of 0.26 .mu.M. Selected compds. gave 20-100% protection of mice from tonic seizures in a sound chamber, at doses of 10-30 mg/kg i.v.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

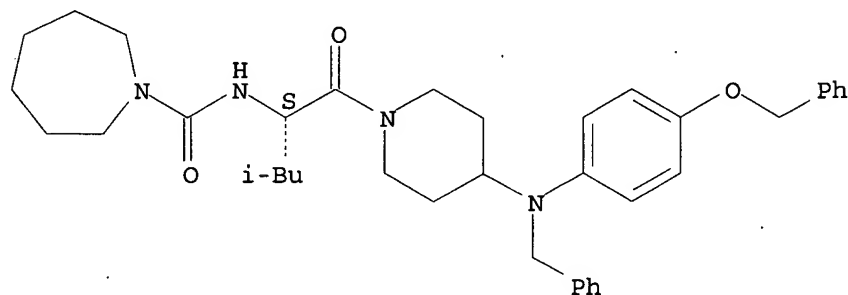
RN 220738-25-0 CAPLUS

CN 1H-Azepine-1-carboxamide, hexahydro-N-[2-[4-[(3-methylbutyl)[4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]-2-oxo-1-(2-pyridinylmethyl)ethyl]- (9CI) (CA INDEX NAME)



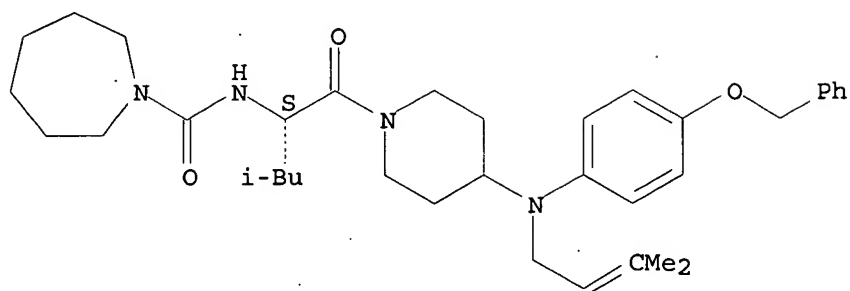
AN 1999:589098 CAPLUS
 DN 131:331730
 TI Synthesis of a Series of 4-Benzyloxylaniline Analogs as Neuronal N-Type Calcium Channel Blockers with Improved Anticonvulsant and Analgesic Properties
 AU Hu, Lain-Yen; Ryder, Todd R.; Rafferty, Michael F.; Feng, M. Rose; Lotarski, Susan M.; Rock, David M.; Sinz, Michael; Stoehr, Sally J.; Taylor, Charles P.; Weber, Mark L.; Bowersox, S. Scott; Miljanich, George P.; Millerman, Elizabeth; Wang, Yong-Xiang; Szoke, Balazs G.
 CS Departments of Chemistry Neuroscience Therapeutics and Pharmacokinetics Dynamics and Metabolism, Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company, Ann Arbor, MI, 48105, USA
 SO Journal of Medicinal Chemistry (1999), 42(20), 4239-4249
 CODEN: JMCMAR; ISSN: 0022-2623
 PB American Chemical Society
 DT Journal
 LA English
 AB In this article, the rationale for the design, synthesis, and biol. evaluation of a series of N-type voltage-sensitive calcium channel (VSCC) blockers is described. N-Type VSCC blockers, such as ziconotide, have shown utility in several models of stroke and pain. Modification of the previously reported lead led to several 4-(4-benzyloxyphenyl)piperidine structures with potent in vitro and in vivo activities. In this series, the most interesting compd., (S)-2-amino-1-{4-[(4-benzyloxy-phenyl)-(3-methyl-but-2-enyl)-amino]-piperidin-1-yl}-4-methyl-pentan-1-one (I), blocked N-type calcium channels (IC₅₀ = 0.67 .mu.M in the IMR32 assay) and was efficacious in the audiogenic DBA/2 seizure mouse model (ED₅₀ = 6 mg/kg, i.v.) as well as the antiwrithing model (ED₅₀ = 6 mg/kg, i.v.). Whole-cell voltage-clamp electrophysiol. expts. demonstrated that compd. I blocked N-type Ca²⁺ channels and Na⁺ channels in superior cervical ganglion neurons at similar concns. Compd. I, which showed superior in vivo efficacy, stands out as an interesting lead for further development of neurotherapeutic agents in this series.
 IT 220737-68-8P 247130-18-3P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
 (synthesis of 4-benzyloxylaniline analogs as neuronal N-type calcium channel blockers with improved anticonvulsant and analgesic properties)
 RN 220737-68-8 CAPLUS
 CN 1H-Azepine-1-carboxamide, hexahydro-N-[(1S)-3-methyl-1-[[4-[(4-(phenylmethoxy)phenyl](phenylmethyl)amino)-1-piperidinyl]carbonyl]butyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 247130-18-3 CAPLUS
 CN 1H-Azepine-1-carboxamide, hexahydro-N-[(1S)-3-methyl-1-[[4-[(3-methyl-2-butenyl)[4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]carbonyl]butyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 220737-64-4P 250236-95-4P 250236-97-6P

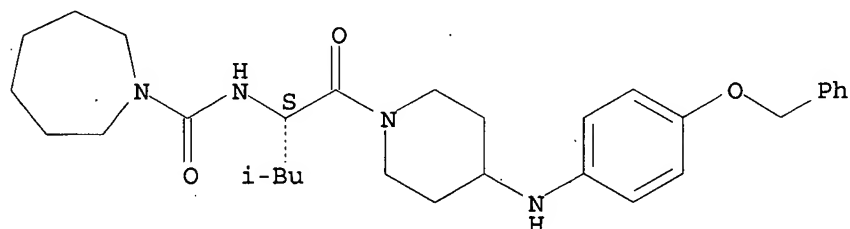
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(synthesis of 4-benzyloxyaniline analogs as neuronal N-type calcium channel blockers with improved anticonvulsant and analgesic properties)

RN 220737-64-4 CAPLUS

CN 1H-Azepine-1-carboxamide, hexahydro-N-[(1S)-3-methyl-1-[[4-[[4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]carbonyl]butyl]- (9CI) (CA INDEX NAME)

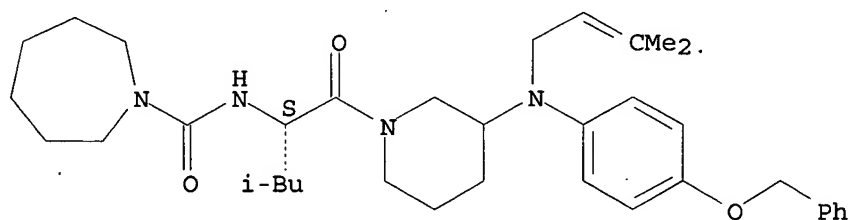
Absolute stereochemistry.



RN 250236-95-4 CAPLUS

CN 1H-Azepine-1-carboxamide, hexahydro-N-[(1S)-3-methyl-1-[[3-[(3-methyl-2-butenyl)4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]carbonyl]butyl]- (9CI) (CA INDEX NAME)

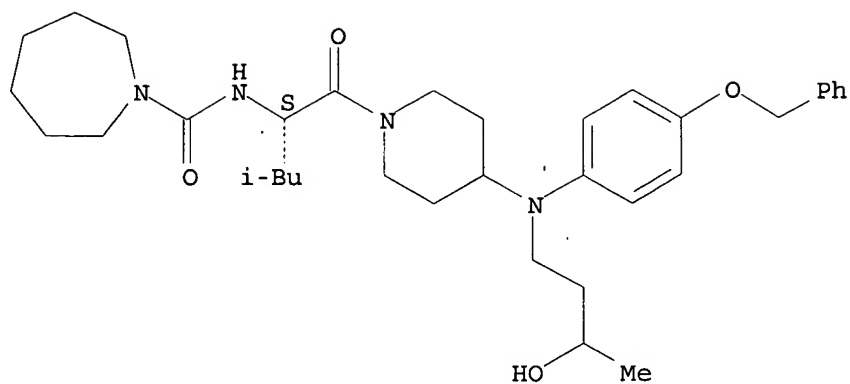
Absolute stereochemistry.



RN 250236-97-6 CAPLUS

CN 1H-Azepine-1-carboxamide, hexahydro-N-[(1S)-1-[[4-[(3-hydroxybutyl)4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 220737-67-7P

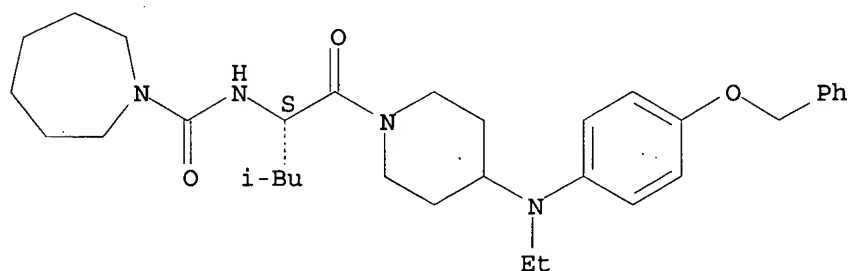
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of 4-benzyloxyaniline analogs as neuronal N-type calcium channel blockers with improved anticonvulsant and analgesic properties)

RN 220737-67-7 CAPLUS

CN 1H-Azepine-1-carboxamide, N-[(1S)-1-[[4-[ethyl[4-(phenylmethoxy)phenyl]amino]-1-piperidinyl]carbonyl]-3-methylbutyl]hexahydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

(95-92-1/RN)
 L2 240 (100-07-2/BI OR 100-09-4/BI OR 1073-29-6/BI OR 108-95-2/BI OR
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 OR 127806-46-6/BI OR 135-02-4/BI OR 138891-54-0/BI OR 141-97-9/B
 I OR 141518-55-0/BI OR 142121-93-5/BI OR 142121-94-6/BI OR 143-3
 3-9/BI OR 14675-99-1/BI OR 150-19-6/BI OR 150-76-5/BI OR 151-50-
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=> s l2 and indol?

525003 INDOL?

L3 39 L2 AND INDOL?

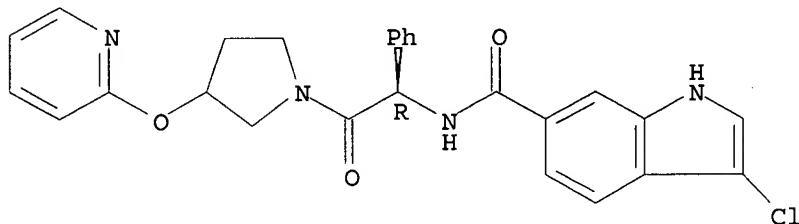
=> d scan

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS

IN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(2-
 pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)

MF C26 H23 Cl N4 O3

Absolute stereochemistry.



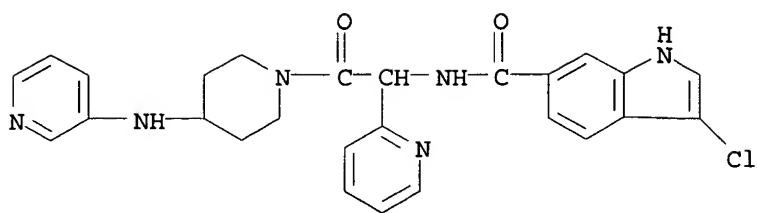
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS

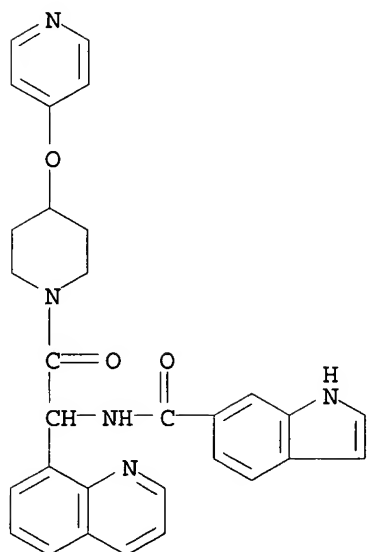
IN 1H-Indole-6-carboxamide, 3-chloro-N-[2-oxo-1-(2-pyridinyl)-2-[4-(3-
 pyridinylamino)-1-piperidinyl]ethyl]-, dihydrochloride (9CI)

MF C26 H25 Cl N6 O2 . 2 Cl H



● 2 HCl

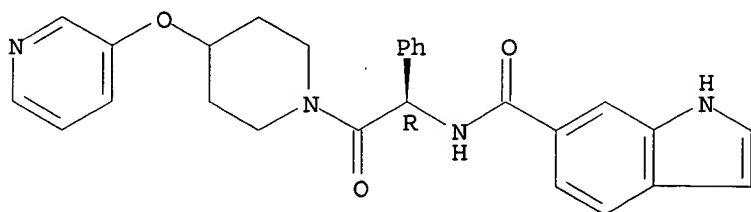
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[2-oxo-2-[4-(4-pyridinyloxy)-1-piperidinyl]-1-(8-quinolinyl)ethyl]-, monohydrochloride (9CI)
 MF C30 H27 N5 O3 . Cl H



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(3-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)
 MF C27 H26 N4 O3

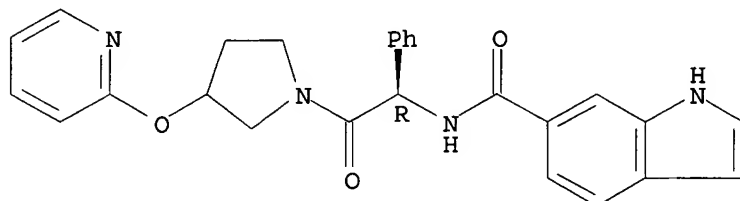
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(2-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)
MF C26 H24 N4 O3

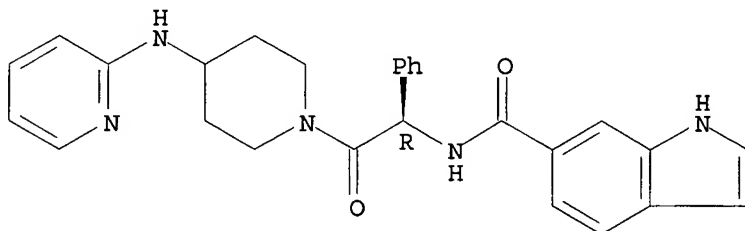
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(2-pyridinylamino)-1-piperidinyl]ethyl]- (9CI)
MF C27 H27 N5 O2
CI COM

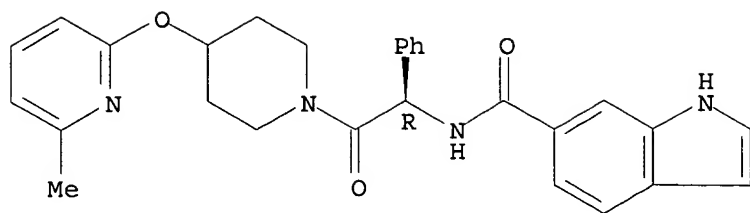
Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1H-Indole-6-carboxamide, N-[(1R)-2-[4-[(6-methyl-2-pyridinyl)oxy]-1-piperidinyl]-2-oxo-1-phenylethyl]-, monohydrochloride (9CI)
MF C28 H28 N4 O3 . Cl H

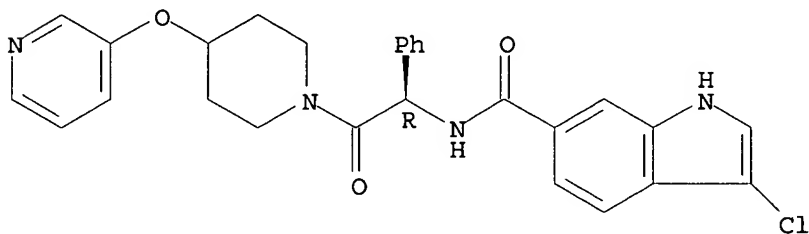
Absolute stereochemistry.



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[4-(3-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)
 MF C27 H25 Cl N4 O3

Absolute stereochemistry.

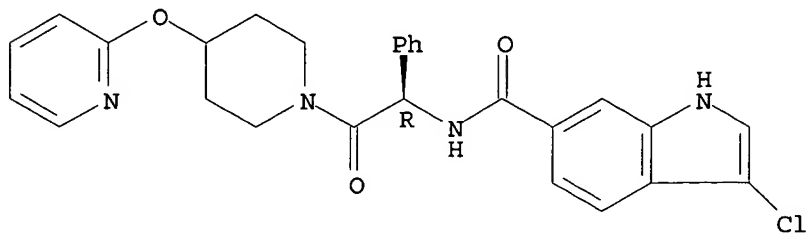


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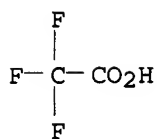
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[4-(2-pyridinyloxy)-1-piperidinyl]ethyl]-, mono(trifluoroacetate) (9CI)
 MF C27 H25 Cl N4 O3 . C2 H F3 O2

CM 1

Absolute stereochemistry.

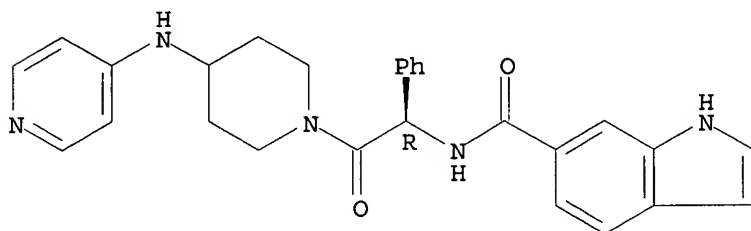


CM 2



L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinylamino)-1-piperidinyl]ethyl]- (9CI)
 MF C27 H27 N5 O2
 CI COM

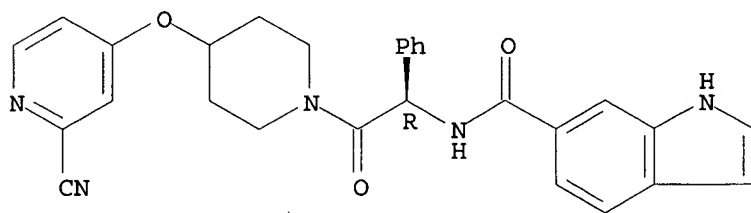
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[(1R)-2-[4-[(2-cyano-4-pyridinyl)oxy]-1-piperidinyl]-2-oxo-1-phenylethyl]-, monohydrochloride (9CI)
 MF C28 H25 N5 O3 . Cl H

Absolute stereochemistry.

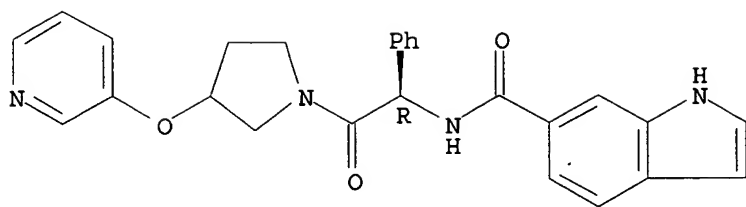


● HCl

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)
 MF C26 H24 N4 O3

Absolute stereochemistry.

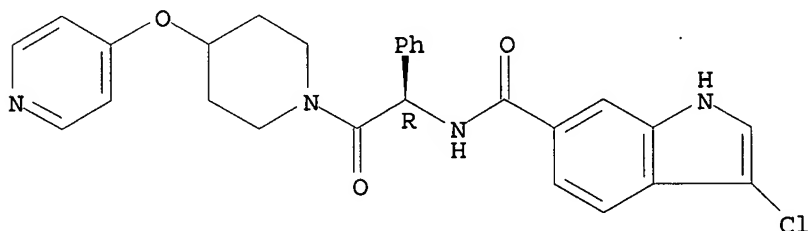


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

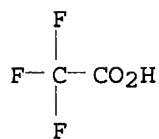
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]-, mono(trifluoroacetate) (9CI)
 MF C27 H25 Cl N4 O3 . C2 H F3 O2

CM 1

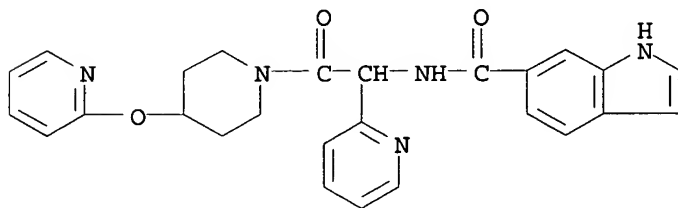
Absolute stereochemistry.



CM 2



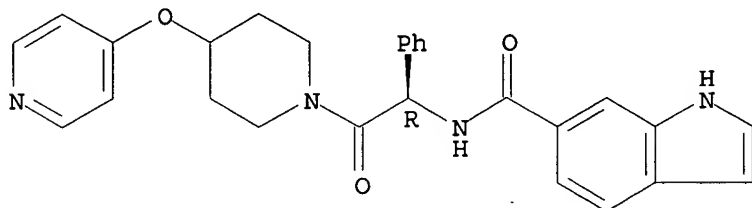
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[2-oxo-1-(2-pyridinyl)-2-[4-(2-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)
 MF C26 H25 N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]-, monohydrochloride (9CI)
MF C27 H26 N4 O3 . Cl H

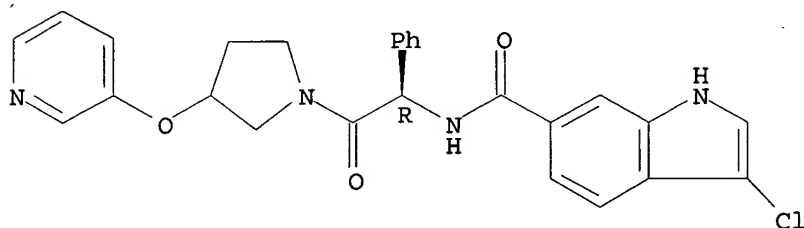
Absolute stereochemistry.



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)
MF C26 H23 Cl N4 O3

Absolute stereochemistry.

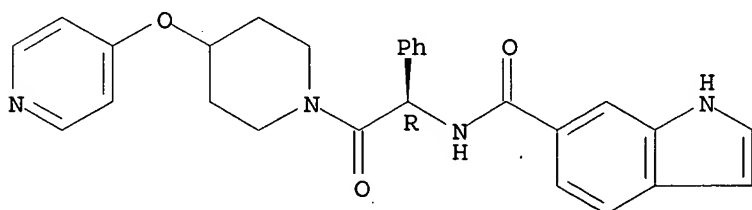


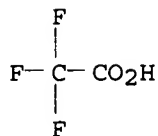
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]-, mono(trifluoroacetate) (9CI)
MF C27 H26 N4 O3 . C2 H F3 O2

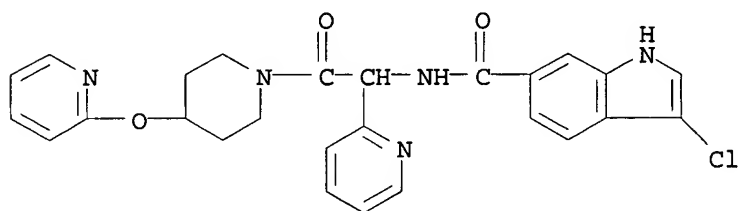
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Absolute stereochemistry.





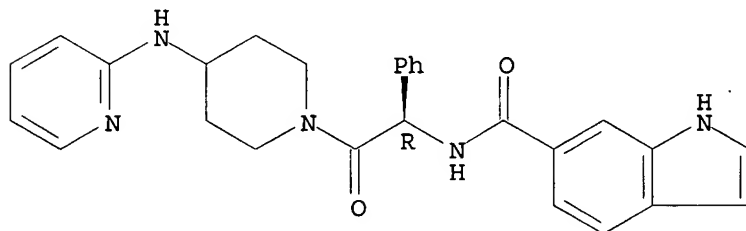
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-chloro-N-[2-oxo-1-(2-pyridinyl)-2-[4-(2-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)
 MF C26 H24 Cl N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(2-pyridinylamino)-1-piperidinyl]ethyl]-, monohydrochloride (9CI)
 MF C27 H27 N5 O2 . Cl H

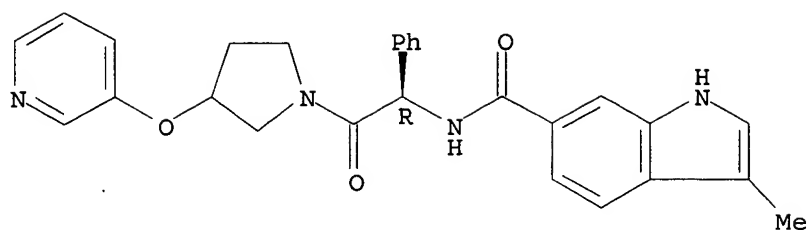
Absolute stereochemistry. Rotation (-).



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-methyl-N-[(1R)-2-oxo-1-phenyl-2-[3-(3-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)
 MF C27 H26 N4 O3

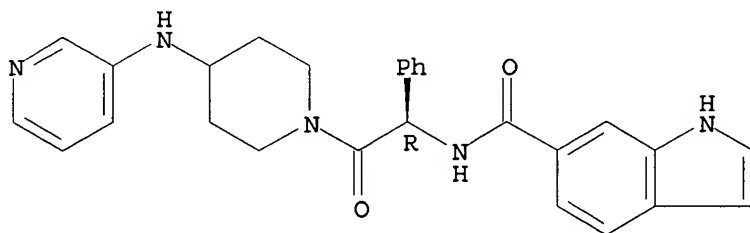
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(3-pyridinylamino)-1-piperidinyl]ethyl]- (9CI)
 MF C27 H27 N5 O2

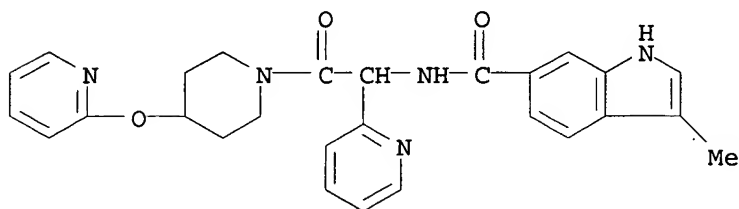
Absolute stereochemistry.



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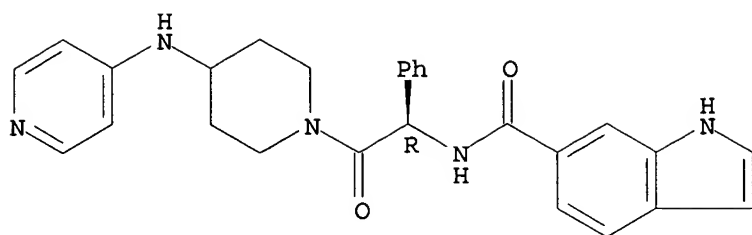
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-methyl-N-[2-oxo-1-(2-pyridinyloxy)-2-[4-(2-pyridinylamino)-1-piperidinyl]ethyl]- (9CI)
 MF C27 H27 N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinylamino)-1-piperidinyl]ethyl]-, monohydrochloride (9CI)
 MF C27 H27 N5 O2 . Cl H

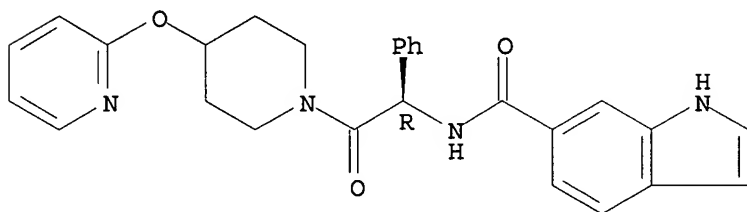
Absolute stereochemistry.



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(2-pyridinyloxy)-
 1-piperidinyl]ethyl]- (9CI)
 MF C27 H26 N4 O3

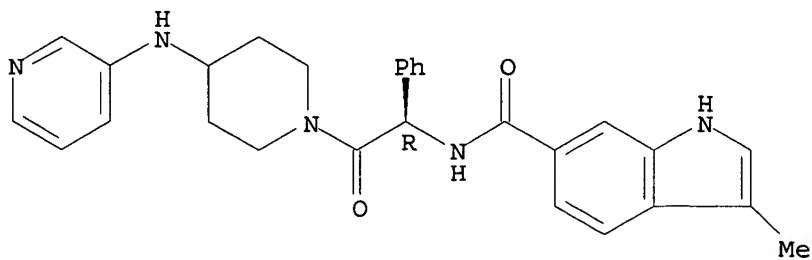
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

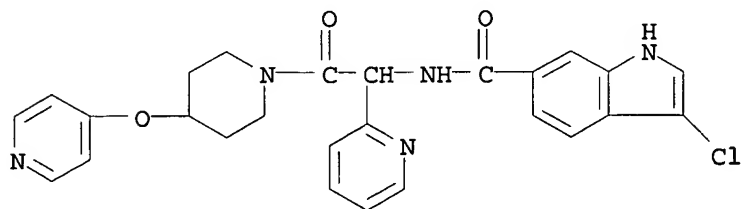
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-methyl-N-[(1R)-2-oxo-1-phenyl-2-[4-(3-
 pyridinylamino)-1-piperidinyl]ethyl]- (9CI)
 MF C28 H29 N5 O2

Absolute stereochemistry.



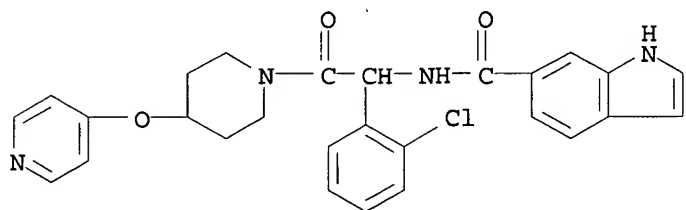
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-chloro-N-[2-oxo-1-(2-pyridinyl)-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)
 MF C26 H24 Cl N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

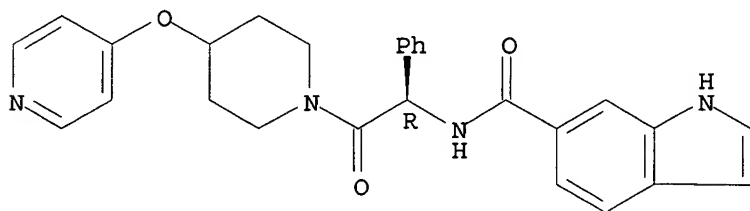
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[1-(2-chlorophenyl)-2-oxo-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)
 MF C27 H25 Cl N4 O3
 CI COM



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)
 MF C27 H26 N4 O3
 CI COM

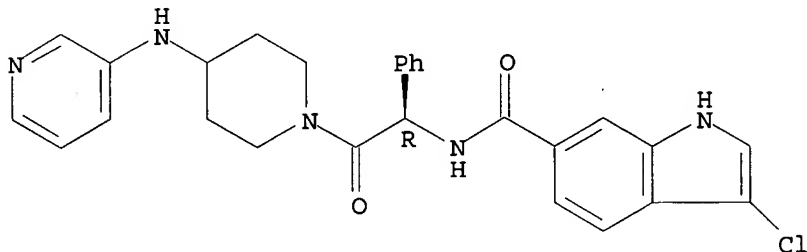
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

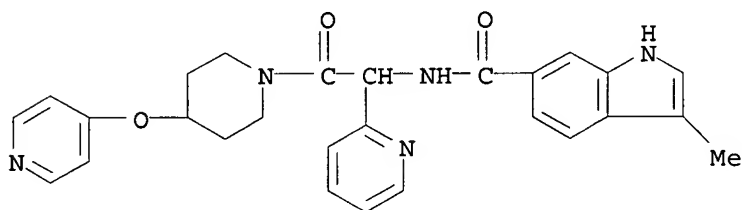
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 MF C27 H26 Cl N5 O2

Absolute stereochemistry.



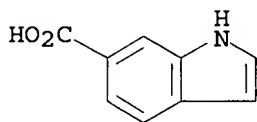
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L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-methyl-N-[2-oxo-1-(2-pyridinyl)-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)
 MF C27 H27 N5 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxylic acid (9CI)
 MF C9 H7 N O2



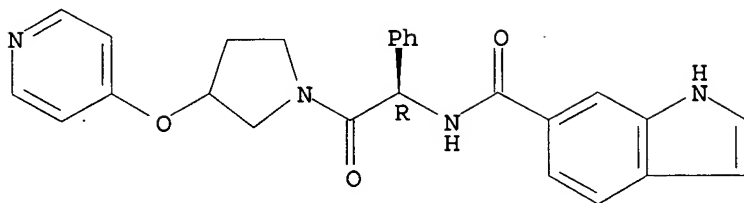
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):10

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)

MF C26 H24 N4 O3

Absolute stereochemistry.

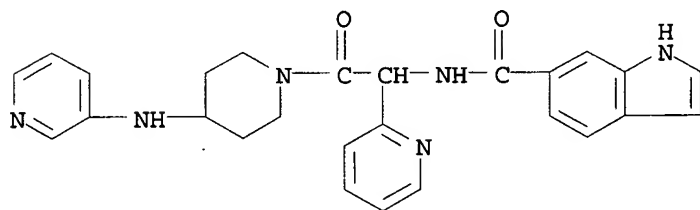


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS

IN 1H-Indole-6-carboxamide, N-[2-oxo-1-(2-pyridinyl)-2-[4-(3-pyridinylamino)-1-piperidinyl]ethyl]-, dihydrochloride (9CI)

MF C26 H26 N6 O2 . 2 Cl H

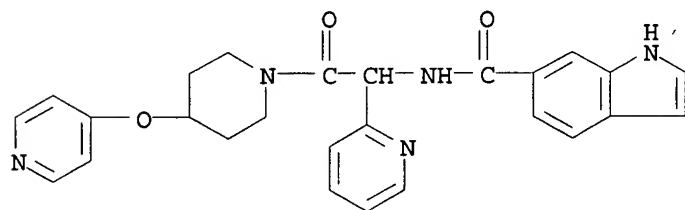


● 2 HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS

IN 1H-Indole-6-carboxamide, N-[2-oxo-1-(2-pyridinyl)-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]- (9CI)

MF C26 H25 N5 O3

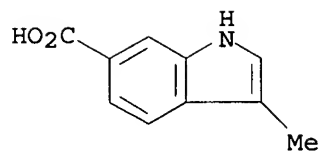


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L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS

IN 1H-Indole-6-carboxylic acid, 3-methyl- (9CI)

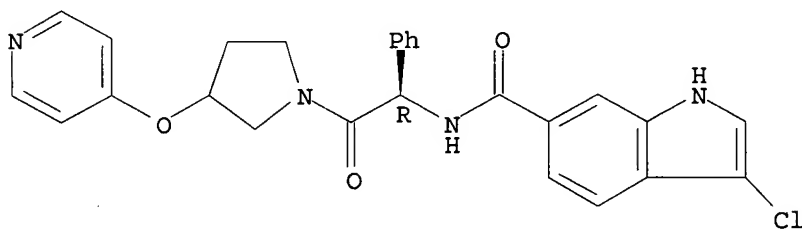
MF C10 H9 N O2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

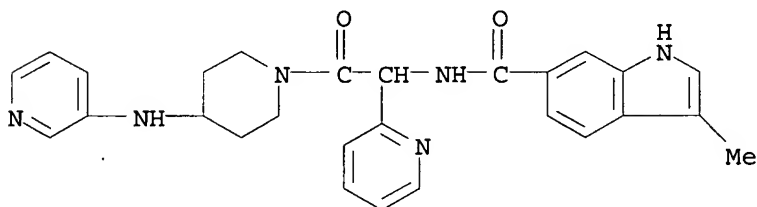
L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, 3-chloro-N-[(1R)-2-oxo-1-phenyl-2-[3-(4-pyridinyloxy)-1-pyrrolidinyl]ethyl]- (9CI)
 MF C26 H23 Cl N4 O3

Absolute stereochemistry.



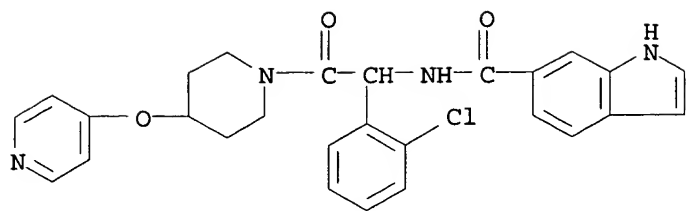
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L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
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 MF C27 H28 N6 O2



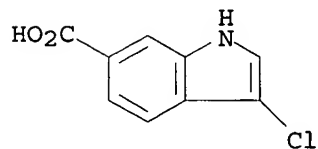
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxamide, N-[1-(2-chlorophenyl)-2-oxo-2-[4-(4-pyridinyloxy)-1-piperidinyl]ethyl]-, monohydrochloride (9CI)
 MF C27 H25 Cl N4 O3 . Cl H



● HCl

L3 39 ANSWERS REGISTRY COPYRIGHT 2003 ACS
 IN 1H-Indole-6-carboxylic acid, 3-chloro- (9CI)
 MF C9 H6 Cl N O2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

=> s wo200196296/pn
L2 2 WO200196296/PN
(WO2001096296/PN)

=> d bib 1-2

L2 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
AN 2001:923758 CAPLUS
DN 136:37946
TI Preparation of amino acid derivatives as serine protease inhibitors
IN Liebeschuetz, John Walter; Murray, Christopher William; Young, Stephen
Clinton; Camp, Nicholas Paul; Jones, Stuart Donald; Wylie, William
Alexander; Masters, John Joseph; Wiley, Michael Robert; Sheehan, Scott
Martin; Engel, David Birenbaum; Watson, Brian Morgan
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 142 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001096296	A1	20011220	WO 2001-GB2541	20010612 <--
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	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
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PRAI	WO 2000-GB2302	W	20000613		
	GB 2000-30303	A	20001213		
	GB 1999-13823	A	19990614		
	US 1999-142064P	P	19990702		
	GB 1999-18741	A	19990809		
	GB 1999-29553	A	19991214		

OS MARPAT 136:37946

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
AN 2000:900614 CAPLUS
DN 134:56958
TI Preparation of amino acid derivatives as serine protease inhibitors
IN Liebeschuetz, John Walter; Lyons, Amanda Jane; Murray, Christopher
William; Rimmer, Andrew David; Young, Stephen Clinton; Camp, Nicholas
Paul; Jones, Stuart Donald; Morgan, Phillip John; Richards, Simon James;
Wylie, William Alexander; Masters, John Joseph; Wiley, Michael Robert
PA Eli Lilly and Company, USA; Protherics Molecular Design Limited

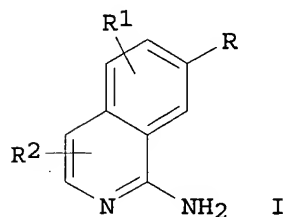
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	WO	2001-GB2572	W	20010612
OS	MARPAT	134:56958		

SO PCT Int. Appl., 261 pp.
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 DT Patent
 LA English
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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000076971	A2	20001221	WO 2000-GB2302	20000613
	WO 2000076971	A3	20010802		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
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WO	2001096323	A1	20011220	WO 2001-GB2553	20010612
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US	2002151724	A1	20021017	US 2002-30186	20020204

AN 1999:184268 CAPLUS
 DN 130:223587
 TI 1-amino-7-isoquinoline derivatives as serine protease inhibitors
 IN Liebeschuetz, John Walter; Wylie, William Alexander; Waszkowycz, Bohdan; Murray, Christopher William; Rimmer, Andrew David; Welsh, Pauline Mary; Jones, Stuart Donald; Roscoe, Jonathan Michael Ernest; Young, Stephen Clinton; Morgan, Phillip John; Camp, Nicholas Paul; Crew, Andrew Philip Austin
 PA Proteus Molecular Design Ltd., UK
 SO PCT Int. Appl., 89 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 13

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PI	WO 9911657	A1	19990311	WO 1998-GB2600	19980828 <--
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	US 6262069	B1	20010717	US 2000-485677	20000225
	US 2002040144	A1	20020404	US 2001-865418	20010529
	US 6420438	B1	20020716	US 2000-865418	20010529
PRAI	GB 1997-18392	A	19970829		
	GB 1998-3173	A	19980213		
	WO 1998-GB2600	W	19980828		
	US 2000-485677	A1	20000225		
OS	MARPAT 130:223587				
GI					



AB Aminoisoquinoline amino acid derivs. I [R1 = H, halo, cyano, nitro, hydroxy, amino, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, thiol, alkylthio, aminosulfonyl, alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or alkylamino (optionally substituted); R2 = H, halo, Me, amino, hydroxy, or oxo; and R is X-X-Y(R7)-L-Lp(D)n, where each X independently is a C, N, O or S atom or a CO, CR1, CR12 or NR1 group; Y is a nitrogen atom or a CR1 group or Y and L taken together form a cyclic group; R7 is a lipophilic group selected from alkyl, alkenyl, mono- or bi-cycloalkyl, aryl, heteroaryl, mono- or bicycloalkylalkyl, mono- or bicycloalkylalkenyl, aralkyl, heteroaryl-alkyl, arylalkenyl, heteroarylalkenyl, all optionally

substituted by a group R1; L is an org. linker group contg. 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic group; Lp is a lipophilic org. group selected from alkyl, heterocyclic, alkenyl, alkaryl, cycloalkyl, polycycloalkyl, cycloalkenyl, aryl, aralkyl or haloalkyl group or a combination of two or more such groups optionally substituted by one or more of oxa, thia, aza or R1 groups; D is a hydrogen bond donor group; and n is 0, 1, or 2] or their 3,4-dihydro derivs. were prepd. as serine protease inhibitors. Thus, 1-aminoisoquinolin-7-oyl-D-phenylglycine-4-methoxybenzylamide was prepd. by amidation of Boc-D-phenylglycine with 4-methylbenzylamine, followed by deprotection and coupling with 1-aminoisoquinoline-7-carboxylic acid trifluoroacetate.

IT 221049-84-9P 221049-99-6P 221050-30-2P

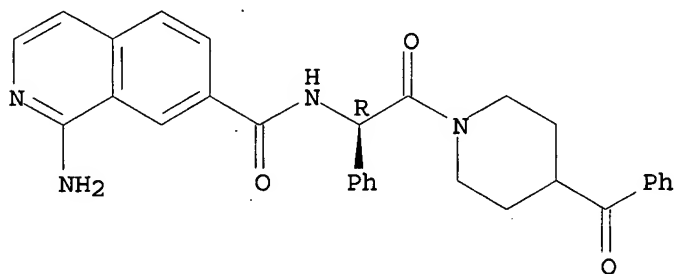
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of aminoisoquinoline peptidyl derivs. as serine protease inhibitors)

RN 221049-84-9 CAPLUS

CN 7-Isoquinolinecarboxamide, 1-amino-N-[(1R)-2-(4-benzoyl-1-piperidiny)-2-oxo-1-phenylethyl]- (9CI) (CA INDEX NAME)

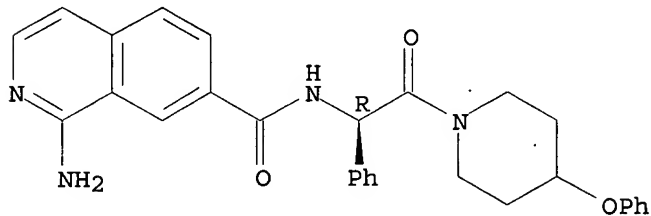
Absolute stereochemistry.



RN 221049-99-6 CAPLUS

CN 7-Isoquinolinecarboxamide, 1-amino-N-[(1R)-2-oxo-2-(4-phenoxy-1-piperidiny)-1-phenylethyl]- (9CI) (CA INDEX NAME)

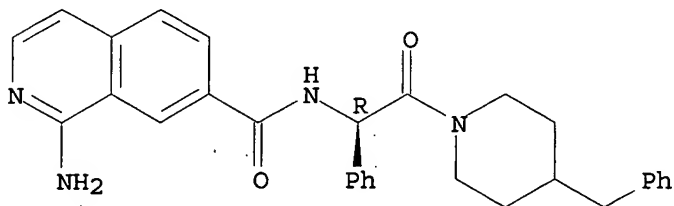
Absolute stereochemistry.

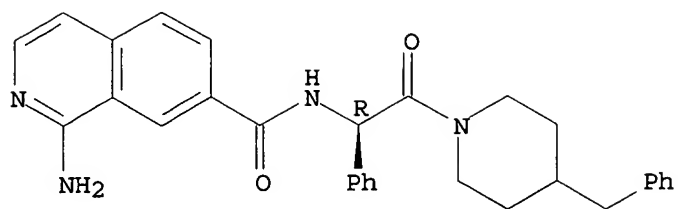


RN 221050-30-2 CAPLUS

CN 7-Isoquinolinecarboxamide, 1-amino-N-[(1R)-2-oxo-1-phenyl-2-[4-(phenylmethyl)-1-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.





RE.CNT 12

THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT